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NEWS	30	MAY 14	RDISCLOSURE on STN Easy enhanced with new search and display fields
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L2        3385 K1 AND ANTIBOD?

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L3         144 L2 AND COMBINATION

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L6   ANSWER 1 OF 3     MEDLINE on STN                    DUPLICATE 1
95403469.    PubMed ID: 7673253.   Heregulin activation of extracellular
     acidification in mammary carcinoma cells is associated with expression of
     HER2 and HER3. Chan S D; Antoniucci D M; Fok K S; Alajoki M L; Harkins R
     N; Thompson S A; Wada H G. (Molecular Devices Corporation, Sunnyvale,
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California 94089, USA.) The Journal of biological chemistry, (1995 Sep 22) Vol. 270, No. 38, pp. 22608-13. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB HER2, the erbB-2/neu proto-oncogene product, is a 185-kDa transmembrane glycoprotein related to the epidermal growth factor receptor. Overexpression of HER2 was reported in several human adenocarcinomas, including mammary and ovarian carcinomas. A family of glycoproteins, the heregulin/neu differentiation factors, was characterized and implicated as the ligands for HER2. Recently, it has been shown that HER2 alone is not sufficient to reconstitute high affinity heregulin receptors and that HER3 or HER4 may be the required components of the heregulin receptors on mammary carcinoma cells (Sliwkowski, M.X., Schaefer, G., Akita, R.W., Lofgren, J.A., Fitzpatrick, V.D., Nuijens, A., Fendly, B.M., Cerione, R.A., Vandlen, R.L., and Carraway, K.L., III (1994) J. Biol. Chemical 269, 14661-14665; Plowman, G.D., Green, J.M., Culouscou, J.-M., Carlton, G.W., Rothwell, V.M., and Buckley, W. (1993) Nature 366, 473-475). Using the Cytosensor to measure the extracellular acidification rate, we have examined the effects of recombinant human heregulin-alpha on three mammary carcinoma cell lines expressing HER2 (MDA-MB-453, SK-BR-3, and MCF-7), an ovarian carcinoma cell line expressing HER2 (SK-OV-3), and CHO-K1 and 293-EBNA cells stably transfected with HER2. By reverse transcription polymerase chain reaction and Western blotting, we found that the breast cells also express HER3 and that the ovarian line co-expresses the HER4 message. A dramatic increase in the acidification rate was observed for the mammary carcinoma cells co-expressing high levels of HER2 and HER3. In contrast, the ovarian cells expressing high levels of HER2 and low levels of HER4 or CHO-K1 and 293-EBNA cells expressing HER2 alone were not responsive to heregulin. When these same transfected cells were exposed to monoclonal anti-HER2 antibody followed by anti-IgG to cause aggregation of the HER2 molecules, an increase in the acidification rate was observed, indicating coupling of transfected HER2 to the signal transduction pathway. Transfection of HER2 into MCF-7 cells, on the other hand, gave 4-fold enhanced acidification responses. These data, together with the previously reported high affinity heregulin binding and activation of tyrosine phosphorylation in HER2 and HER3 co-transfected cells support the role of HER2 and HER3 as components of the heregulin receptor in breast cells.

L6 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN

1995:254144 Document No. 122:47384 Keratinocyte growth factor receptor ligands induce transforming growth factor α expression and activate the epidermal growth factor receptor signaling pathway in cultured epidermal keratinocytes. Dlugosz, Andrzej A.; Cheng, Christina; Denning, Mitchell F.; Dempsey, Peter J.; Coffey, Robert J., Jr.; Yuspa, Stuart H. (Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Cancer Institute, Bethesda, MD, 20892, USA). Cell Growth & Differentiation, 5(12), 1283-92 (English) 1994. CODEN: CGDIE7. ISSN: 1044-9523. Publisher: American Association for Cancer Research.

AB EGF receptor (EGFR) ligands are fundamental regulators of epithelial growth, differentiation, and neoplastic transformation. In addition to being potent mitogens for murine epidermal keratinocytes in vitro, transforming growth factor α (TGFα) and EGF elicit distinctive changes in keratin expression: Ca2+-mediated induction of the differentiation-specific keratins K1 and K10 is blocked, while simple epithelial keratins K8 and K18 are expressed aberrantly (C. Cheng et al., 1993). We have evaluated several addnl. growth factors to determine the specificity of this response for EGFR ligands. TGFα, keratinocyte growth factor (KGF), and acidic FGF (aFGF), but not basic FGF (bFGF) or IGF-I, block Ca2+-mediated expression of K1 while inducing K8. Since KGF and aFGF (but not bFGF) are ligands for the KGF receptor (KGFR), we explored the possibility that the TGFα/EGFR pathway is an intermediary in

signaling through the KGFR. TGFα mRNA was increased in cells treated with KGF, aFGF, or TGFα but not bFGF or IGF-I. Similar changes were detected at the protein level; TGFα in conditioned medium (CM) from control, KGF-, TGFα-, and aFGF-treated cultures was 54, 365, 146, and 120 pg/mL, resp. KGF and TGFα also increased expression of cell-associated TGFα measured in keratinocyte lysates. KGF increased TGFα secretion and mRNA levels in human as well as mouse keratinocytes. CM from KGF-treated cultures stimulated cell growth when added to cultures of normal keratinocytes. Preincubation with neutralizing antibodies or both TGFα and KGF, but not KGF antibody alone, blocked cell growth in cultures treated with KGF CM, suggesting that the predominant keratinocyte mitogen in KGF CM is TGFα. In support of this hypothesis, treatment of keratinocytes for 5 min with either KGF CM or purified TGFα resulted in EGFR autophosphorylation. Furthermore, after .apprx.24 h, KGF as well as TGFα induced EGFR down-regulation based on Western blot anal. and 125I-EGF binding. Induction of TGFα in KGF-treated keratinocytes, coupled to activation and down-modulation of the EGFR, suggests that TGFα may be a proximal effector of KGF action for at least certain aspects of epidermal growth and differentiation.

L6 ANSWER 3 OF 3 MEDLINE on STN

92290622. PubMed ID: 1351045. Frequent expression of the tumor antigen CAK1 in squamous-cell carcinomas. Chang K; Pastan I; Willingham M C. (Laboratory of Molecular Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.) International journal of cancer. Journal international du cancer, (1992 Jun 19) Vol. 51, No. 4, pp. 548-54. Journal code: 0042124. ISSN: 0020-7136. Pub. country: United States. Language: English.

AB K1 is a murine monoclonal antibody (MAb) derived from a hybridoma generated by the fusion of splenocytes of BALB/c mice immunized with a human ovarian tumor cell line, OVCAR-3. This antibody reacts strongly with epithelial ovarian tumors and mesotheliomas. The antigen recognized by MAb K1, designated CAK1, has recently been characterized as a 40-kDa protein probably anchored to the cell surface by glycosyl-phosphatidylinositol. Using immunoperoxidase histochemical methods, we examined 37 squamous-cell carcinoma (SqCC) samples from cervix, lung, esophagus and other origins, and 12 normal squamous epithelia of the cervix and esophagus for their reactivity with MAb K1. Of the SqCC specimens, 81% showed K1 reactivity with variable intensity, but none of 12 normal tissue samples of squamous epithelia did so. Two patterns of CAK1 expression in tumor samples were found, i.e., a heterogeneous pattern with strong intensity, and a homogeneous pattern with weak intensity. Three carcinomas in situ of the larynx, vulva and esophagus were moderately positive with K1, suggesting that CAK1 antigen may occur in the early stage of carcinogenesis of SqCC. The expression of CAK1 was also compared with expression of CA125, HER-2/neu, p53 and P-glycoprotein, and MAb K1 was found to react most consistently with SqCC. Since K1 reacts with a majority of cervical and esophageal carcinomas but has no detectable reactivity in normal epithelia of the cervix uteri and esophagus, MAb K1 could be of value as a reagent to help distinguish between normal and neoplastic cells on sections as well as in cytological samples.

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L9 ANSWER 1 OF 7 MEDLINE on STN DUPLICATE 1
2006718900. PubMed ID: 16886908. Selection and characterization of an internalizing epidermal-growth-factor-receptor antibody. Zhao Xiaorong; Dai Wentao; Cao Limin; Zhu Huifen; Yu Yihan; Ye Qing; Wang Min; Dai Wei; Lei Ping; Shen Guanxin. (Laboratory of Molecular and Immuno-Pharmacology, Department of Immunology Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, People's Republic of China.) Biotechnology and applied biochemistry, (2007 Jan) Vol. 46, No. Pt 1, pp. 27-33. Journal code: 8609465. E-ISSN: 1470-8744. Pub. country: England: United Kingdom. Language: English.
AB Antibody-therapeutic agent conjugates to be delivered directly into the cytosol of tumour cells is required for many target-based therapeutic strategies. For this work, a large non-immune phage-display library was used to select internalizing scFv (single chain variable fragment) directed against EGFR (epidermal growth factor receptor), a tyrosine kinase receptor that is overexpressed in a wide range of tumour cells. The CHO-EGFR-GFP1 (where CHO is Chinese-hamster ovary) cell line, a transfected cell line expressing EGFR-GFP (green fluorescent protein) fusion protein on membranes, and the untransfected cell line CHO-K1 were used as EGFR -positive cells and -negative cells respectively in the subtractive selection procedure. A novel human anti-EGFR scFv (F4-scFv) was isolated. F4-scFv bound native EGFR-bearing cell lines and could be internalized, but did not bind EGFR-negative cell lines. The K(D) value of F4-scFv was 472 nM as determined on A431 cells. F4-scFv could be used to target therapeutic agents into tumour cells and was expected to be non-immunogenic in humans. Use of a transfected cell line expressing GFP-tagged receptors allows selection and characterization of antibodies to native receptors without the need for protein expression and purification, significantly speeding up the generation of targeting antibodies.

L9 ANSWER 2 OF 7 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2006:297056 Document No.: PREV200600297498. Directed evolution of the epidermal growth factor receptor extracellular domain for expression in yeast. Kim, Yong-Sung; Bhandari, Rashna; Cochran, Jennifer R.; Kuriyan, John; Wittrup, K. Dane [Reprint Author]. MIT, Div Biol Engn, 400 Main St Bldg 66-552, Cambridge, MA 02139 USA. wittrup@mit.edu. Proteins Structure Function and Bioinformatics, (MAR 1 2006) Vol. 62, No. 4, pp. 1026-1035. CODEN: PSFGEY. ISSN: 0887-3585. Language: English.
AB The extracellular domain of epidermal growth factor receptor (EGFR -ECD) has been engineered through directed evolution and yeast surface display using conformationally-specific monoclonal antibodies (mAbs) as screening probes for proper folding and functional expression in Saccharomyces cerevisiae. An EGFR mutant with four amino acid changes exhibited binding to the conformationally-specific mAbs and human epidermal growth factor, and showed increased soluble secretion efficiency compared with wild-type EGFR. Full-length EGFR containing the mutant EGFR-ECD was functional, as assayed by EGF-dependent autophosphorylation and intracellular MAPK signaling in mammalian cells, and was expressed and localized at the plasma membrane in yeast. This approach should enable engineering of other complex mammalian receptor glycoproteins in yeast for genetic, structural, and biophysical studies.

L9 ANSWER 3 OF 7 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights

reserved on STN DUPLICATE 2
2006251624 EMBASE The efficacy of alginate encapsulated CHO-K1 single chain-TRAIL producer cells in the treatment of brain tumors. Kuijlen J.M.A.; de Haan B.J.; Helfrich W.; de Boer J.-F.; Samplonius D.; Mooij J.J.A.; de Vos P.. J.M.A. Kuijlen, Department of Neurosurgery, University Medical Centre Groningen, University of Groningen, Hanzeplein 1, 9700 RB Groningen, Netherlands. j.m.a.kuijlen@nchir.umcg.nl. Journal of Neuro-Oncology Vol. 78, No. 1, pp. 31-39 2006.
Refs: 23.
ISSN: 0167-594X. E-ISSN: 1573-7373. CODEN: JNODD2
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20060615. Last Updated on STN: 20060615
AB Object: Patients with astrocytic tumors in the central nervous system (CNS) have low survival rates despite surgery and radiotherapy. Innovative therapies and strategies must be developed to prolong survival of these patients. The alginate microencapsulation method, used to continuously release a certain cytotoxic agent in the vicinity of the tumor, is such a novel therapeutic strategy. The biological functionality of the apoptosis inducing scFv425:sTRAIL protein, which was released through the microencapsulation method, was studied in vitro. Analysis of the intracerebral biocompatibility of alginate capsules was performed by implantation of empty alginate capsules in the brain of mice. Method: Chinese Hamster Ovary cells (CHO-K1) were recombinantly engineered to produce the single chain anti-EGFR-sTRAIL protein (scFv425:sTRAIL). The CHO-K1 producer cells were encapsulated in an alginate capsule with a semi-permeable membrane through which the scFv425:sTRAIL protein could be released. Results: In vitro studies show maintained biological functionality of the released scFv425:sTRAIL protein. There was no immunological tissue response detectable after intracerebral implantation of the alginate capsules in mice brains. Conclusion: Biological functionality of the produced scFv425:sTRAIL protein is maintained and intracerebral biocompatibility of the capsules is warranted. Alginate encapsulation of CHO-K1 - scFv425:sTRAIL - producer cells and subsequently their intracerebral implantation is technically feasible. This study justifies further in vivo experiments. .COPYRGT. Springer Science+Business Media, Inc. 2006.

L9 ANSWER 4 OF 7 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN
2001:331622 The Genuine Article (R) Number: 422QK. Proliferation and differentiation of the keratinocytes in hyperplastic epidermis overlying dermatofibroma - Immunohistochemical characterization.. Han K H; Huh C H; Cho K H (Reprint). Seoul Natl Univ Hosp, Dept Dermatol, Chongno Gu, 28 Yongon Dong, Seoul 110744, South Korea (Reprint); Seoul Natl Univ Hosp, Clin Res Inst, Lab Cutaneous Aging Res, Chongno Gu, Seoul 110744, South Korea; Seoul Natl Univ, Coll Med, Dept Dermatol, Seoul 110744, South Korea . AMERICAN JOURNAL OF DERMATOPATHOLOGY (APR 2001) Vol. 23, No. 2, pp. 90-98. ISSN: 0193-1091. Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Epidermal changes overlying dermatofibromas (DFs) have been described as ranging from psoriasiform simple hyperplasia to basaloid hyperplasia sometimes morphologically indistinguishable from superficial basal cell carcinoma (BCC). To characterize epidelmal hyperplasia overlying DFs and to determine its association with the disease process, we examined 30 cases of DF showing hyperplastic epidermis. We used nine immunohistochemical markers associated with keratinocyte proliferation or differentiation. In DFs, the dermal metallothionein (MT) expression and immunophenotypic changes with regard to epidermal differentiation varied depending on the stage of lesional evolution of the DFs. Immunostaining for epidermal growth factor receptor (EGFR), MT, and keratin 6 (K6) increased in simple hyperplastic epidermis (SHE) overlying DFs (n =

11), whereas it gradually diminished in basaloid hyperplastic epidermis (BHE) overlying DFs (n = 19). In SHE, there was a significant increase in K14 expression. Among 19 BHE: cases, 12 showed premature expression of involucrin and delayed appearance of K1 along with aberrant expression of K14. Conversely, the remaining 7 BHE cases showed a pattern of involucrin and K1 similar to that of normal skin coinciding with decreased or absent dermal M7 expression. Loricrin and filaggrin expression in all DFs was the same as that of normal skin. Based on the sparse positivity of Ki-67 in the hyperplastic epidermis overlying DFs, we found that the biologic ability of BHE and SHE was not apparent in the hyperproliferative state observed in psoriasis and BCC. Thee results suggest that the dermal fibrohistiocytic process may trigger the induction of SHE overlying DFs by an unknown mechanism and then mediate both the abnormal keratinocyte differentiation and the transformation of SHE to BHE through the evolution of the dermal lesions.

L9 ANSWER 5 OF 7 MEDLINE on STN

97384952. PubMed ID: 9242447. Targeted disruption of the epidermal growth factor receptor impairs growth of squamous papillomas expressing the v-ras(Ha) oncogene but does not block in vitro keratinocyte responses to oncogenic ras. Dlugosz A A; Hansen L; Cheng C; Alexander N; Denning M F; Threadgill D W; Magnuson T; Coffey R J Jr; Yuspa S H. (Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Cancer Institute, Bethesda, Maryland 20892, USA.) Cancer research, (1997 Aug 1) Vol. 57, No. 15, pp. 3180-8. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB We have assessed the role of epidermal growth factor receptor (EGFR) signaling in biological responses to the v-ras(Ha) oncogene using primary keratinocytes from Egfr -/- mice and wild-type littermates. On the basis of several criteria, Egfr -/- keratinocytes were unresponsive to either acute or chronic exposure to several EGFR ligands but were stimulated to proliferate in response to several other mitogens. Although conditioned medium from primary keratinocytes transduced with v-ras(Ha) retrovirus (v-ras(Ha) keratinocytes) was a potent mitogen for wild-type but not Egfr -/- keratinocytes, v-ras(Ha) transduction of primary keratinocytes of either genotype resulted in a strong mitogenic response, arguing against an obligatory role for EGFR activation in v-ras(Ha)-mediated stimulation of keratinocyte proliferation. Infection with high-titer v-ras(Ha) retrovirus altered the keratin expression pattern in keratinocytes of both genotypes, suppressing differentiation-specific keratins K1 and K10 while activating aberrant expression of K8 and K18. In wild-type but not Egfr -/- cultures, K1 and K10 were also suppressed following infection at lower retroviral titers, presumably as a result of paracrine EGFR activation on uninfected cells present in these cultures. Squamous papillomas produced by grafting Egfr -/- v-ras(Ha) keratinocytes onto nude mice were only 21% of the size of wild-type v-ras(Ha) tumors, and a striking redistribution of S-phase cells was detected by immunostaining for bromodeoxyuridine. In Egfr -/- v-ras(Ha) papillomas, the fraction of total labeled nuclei detected in suprabasal layers was increased from 19 to 39%. In contrast, the basal layer labeling index of Egfr -/- papillomas was reduced to 34%, compared to 43% in wild-type tumors. Our results indicate that, although autocrine EGFR signaling is not required for keratinocyte responses to oncogenic ras in culture or benign tumor formation in nude mouse grafts, disruption of this pathway impairs growth of v-ras(Ha) papillomas by a mechanism that may involve alterations in keratinocyte cell cycle progression and/or migration in vivo.

L9 ANSWER 6 OF 7 MEDLINE on STN DUPLICATE 3

95210161. PubMed ID: 7535082. Keratinocyte growth factor receptor ligands

induce transforming growth factor alpha expression and activate the epidermal growth factor receptor signaling pathway in cultured epidermal keratinocytes. Dlugosz A A; Cheng C; Denning M F; Dempsey P J; Coffey R J Jr; Yuspa S H. (Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Cancer Institute, Bethesda, Maryland 20892.) Cell growth & differentiation : the molecular biology journal of the American Association for Cancer Research, (1994 Dec) Vol. 5, No. 12, pp. 1283-92. Journal code: 9100024. ISSN: 1044-9523. Pub. country: United States. Language: English.

AB Epidermal growth factor receptor (EGFR) ligands are fundamental regulators of epithelial growth, differentiation, and neoplastic transformation. In addition to being potent mitogens for murine epidermal keratinocytes in vitro, transforming growth factor alpha (TGF alpha) and EGF elicit distinctive changes in keratin expression: Ca(2+)-mediated induction of the differentiation-specific keratins K1 and K10 is blocked, while simple epithelial keratins K8 and K18 are expressed aberrantly (C. Cheng et al., Cell Growth, & Differ., 4: 317-327, 1993). We have evaluated several additional growth factors to determine the specificity of this response for EGFR ligands. TGF alpha, keratinocyte growth factor (KGF), and acidic fibroblast growth factor (aFGF), but not basic fibroblast growth factor (bFGF) or insulin-like growth factor type I, block Ca(2+)-mediated expression of K1 while inducing K8. Since KGF and aFGF (but not bFGF) are ligands for the KGF receptor (KGFR), we explored the possibility that the TGF alpha/ EGFR pathway is an intermediary in signaling through the KGFR. TGF alpha mRNA was increased in cells treated with KGF, aFGF, or TGF alpha but not bFGF or insulin-like growth factor type I. Similar changes were detected at the protein level; TGF alpha in conditioned medium (CM) from control, KGF-, TGF alpha-, and aFGF-treated cultures was 54 (+/- 8, SEM), 365 (+/- 50), 146 (+/- 20), and 120 (+/- 50) pg/ml, respectively. KGF and TGF alpha also increased expression of cell-associated TGF alpha measured in keratinocyte lysates. KGF increased TGF alpha secretion and mRNA levels in human as well as mouse keratinocytes. CM from KGF-treated cultures stimulated cell growth when added to cultures of normal keratinocytes. Preincubation with neutralizing antibodies to both TGF alpha and KGF, but not KGF antibody alone, blocked cell growth in cultures treated with KGF CM, suggesting that the predominant keratinocyte mitogen in KGF CM is TGF alpha. In support of this hypothesis, treatment of keratinocytes for 5 min with either KGF CM or purified TGF alpha resulted in EGFR autophosphorylation. Furthermore, after approximately 24 h, KGF as well as TGF alpha induced EGFR down-regulation based on Western blot analysis and 125I-EGF binding. Induction of TGF alpha in KGF-treated keratinocytes, coupled to activation and down-modulation of the EGFR, suggests that TGF alpha may be a proximal effector of KGF action for at least certain aspects of epidermal growth and differentiation.

L9 ANSWER 7 OF 7 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

1993:6287 Document No.: PREV199395006287. Relationships between Ki-67 labelling index, amplification of the epidermal growth factor receptor gene, and prognosis in human glioblastomas. Torp, S. H. [Reprint author]; Helseth, E.; Dalen, A.; Unsgaard, G.. Inst. Cancer Res., Med. Technical Cancer, N-7005 Trondheim, Norway. Acta Neurochirurgica, (1992) Vol. 117, No. 3-4, pp. 182-186.
CODEN: ACNUA5. ISSN: 0001-6268. Language: English.

AB The aim of this study was to determine possible relationships between Ki-67 labelling index (Ki-67 LI), amplification of the epidermal growth factor receptor (EGFR) gene, and prognosis in human glioblastomas. Ki-67 LI was determined on cryosections of biopsy specimens of 20 human glioblastomas with a mouse antihuman Ki-67 monoclonal antibody. Amplification of the EGFR gene was determined by slot blot and Southern blot analyses of DNA extracted

from the tumour biopsies. The Ki-67 LI was higher in the glioblastoma group with EGFR gene amplification (8 tumours, median value of Ki-67 LI 4.2, range 0.4-24.6) than in those without EGFR gene amplification (12 tumours, median value of Ki-67 LI 0.8 range 0.2-11.8) (0.05 p lt 0.01). The glioblastoma patients with Ki-67 LI gt 1.5 (10 tumours) had a statistically significant shorter survival than those with Ki-67 LI KAPPA 1.5 (10 tumours) (p lt 0.05). The glioblastoma patients with EGFR gene amplification, lived shorter time than those without EGFR gene amplification (p gt 0.05).

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L12 151 L11 AND EGFR

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L13 39 L12 AND COMBINATION

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L14 15 DUP REMOVE L13 (24 DUPLICATES REMOVED)

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L14 ANSWER 1 OF 15 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2007:303341 Document No.: PREV200700308469. The combination of lapatinib (GW572016F) and agents targeting the insulin-like growth factor I receptor results in synergistic tumor cell growth inhibition and induction of apoptosis. Rusnak, David W. [Reprint Author]; Kumar, Rakesh; Gilmer, Tona M.. GlaxoSmithKline Inc, Res Triangle Pk, NC USA. Proceedings of the American Association for Cancer Research Annual Meeting, (APR 2007) Vol. 48, pp. 1357.
Meeting Info.: 98th Annual Meeting of the American-Association-for-Cancer-Research. Los Angeles, CA, USA. April 14 -18, 2007. Amer Assoc Canc Res.
ISSN: 0197-016X. Language: English.

L14 ANSWER 2 OF 15 MEDLINE on STN DUPLICATE 1
2007075608. PubMed ID: 17208435. Dual inhibition of ErbB1 (EGFR/HER1) and ErbB2 (HER2/neu). Reid Alison; Vidal Laura; Shaw Heather; de Bono Johann. (Royal Marsden Hospital, The Institute of Cancer Research, Centre for Cancer Therapeutics, Downs Road, Sutton, Surrey SM2 5PT, UK.) European journal of cancer (Oxford, England : 1990), (2007 Feb) Vol. 43, No. 3, pp. 481-9. Electronic Publication: 2007-01-08. Ref: 82.
Journal code: 9005373. ISSN: 0959-8049. Pub. country: England: United Kingdom. Language: English.
AB Targeting of epidermal growth factor receptor (EGFR) and HER2 is a proven anti-cancer strategy. However, heterodimerisation, compensatory 'crosstalk' and redundancy exist in the ErbB network, and there is therefore a sound scientific rationale for dual inhibition of EGFR and HER2. Trials of approved agents in combination, for example trastuzumab and cetuximab, are underway. There is also a new generation of small molecule tyrosine kinase inhibitors (TKIs) and monoclonal

antibodies (mABs) that target two or more ErbB receptors. Lapatinib, a TKI of EGFR and HER2, has shown clinical benefit in trastuzumab refractory breast cancer and is poised for FDA approval. Other agents include BIBW-2992 and HKI-272, irreversible TKIs of EGFR and HER2, and pertuzumab, a heterodimerisation inhibitor of EGFR and HER2.

L14 ANSWER 3 OF 15 MEDLINE on STN DUPLICATE 2

2007098583. PubMed ID: 16738850. Efficient inhibition of EGFR signaling and of tumour growth by antagonistic anti-EFGR Nanobodies. Roovers Rob C; Laeremans Toon; Huang Lieven; De Taeye Severine; Verkleij Arie J; Revets Hilde; de Haard Hans J; van Bergen en Henegouwen Paul M P. (Department of Molecular Cell Biology, Institute of Biomembranes, Utrecht University, Padualaan 8, CH-3584 Utrecht, The Netherlands.) Cancer immunology, immunotherapy : CII, (2007 Mar) Vol. 56, No. 3, pp. 303-317. Journal code: 8605732. ISSN: 0340-7004. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB The development of a number of different solid tumours is associated with over-expression of ErbB1, or the epidermal growth factor receptor (EGFR), and this over-expression is often correlated with poor prognosis of patients. Therefore, this receptor tyrosine kinase is considered to be an attractive target for antibody-based therapy. Indeed, antibodies to the EGFR have already proven their value for the treatment of several solid tumours, especially in combination with chemotherapeutic treatment regimens. Variable domains of camelid heavy chain-only antibodies (called Nanobodies) have superior properties compared with classical antibodies in that they are small, very stable, easy to produce in large quantities and easy to re-format into multi-valent or multi-specific proteins. Furthermore, they can specifically be selected for a desired function by phage antibody display. In this report, we describe the successful selection and the characterisation of antagonistic anti-EGFR Nanobodies. By using a functional selection strategy, Nanobodies that specifically competed for EGF binding to the EGFR were isolated from "immune" phage Nanobody repertoires. The selected antibody fragments were found to efficiently inhibit EGF binding to the EGFR without acting as receptor agonists themselves. In addition, they blocked EGF-mediated signalling and EGF-induced cell proliferation. In an in vivo murine xenograft model, the Nanobodies were effective in delaying the outgrowth of A431-derived solid tumours. This is the first report describing the successful use of untagged Nanobodies for the in vivo treatment of solid tumours. The results show that functional phage antibody selection, coupled to the rational design of Nanobodies, permits the rapid development of novel anti-cancer antibody-based therapeutics.

L14 ANSWER 4 OF 15 EMBASE

2007012849 EMBASE HER-2 and NF-κB as the targets for therapy-resistant breast cancer. Ahmed K.M.; Cao N.; Li J.J.. Dr. J.J. Li, 1279 Civil Engineering Building, 550 Stadium Mall Drive, West Lafayette, IN 47907, United States. jjli@purdue.edu. Anticancer Research Vol. 26, No. 6 B, pp. 4235-4243 2006.
Refs: 106.
ISSN: 0250-7005. CODEN: ANTRD4
Pub. Country: Greece. Language: English. Summary Language: English.
Entered STN: 20070130. Last Updated on STN: 20070130

AB HER-2 (also called ErbB2 or Neu) tyrosine kinase, one of the four members of ErbB receptor family (ErbB1, i.e., EGFR, ErbB2, ErbB3 and ErbB4), plays a critical role in the control of diverse cellular functions involved in differentiation, proliferation, migration and cell survival via multiple signal transduction pathways. Overexpression of

HER-2, observed in HER-2-positive breast cancer patients, is believed to cause the tumor resistance to an array of anti-cancer agents and poor prognosis. Although HER-2 antibodies have shown growth inhibitory effects, more efficient molecular targets against HER-2-mediated tumor resistance need to be developed. The molecular mechanisms underlying HER-2-mediated tumor resistance, especially the connections between HER-2 and therapy-resistant signaling networks, need to be further investigated. NF-KB, a key stress transcription factor that can initiate a pro-survival network, was found to be activated in many cancer cells overexpressing HER-2 and to be responsible for the radiation resistance in HER-2 transfected breast cancer cells. Recent findings in literature and data from this laboratory suggest a possible co-operation between HER-2 and NF-κB in signaling tumor resistance to radiotherapy. This review will discuss the mechanisms of HER-2 mediated NF-κB signaling pathway and potential target for therapeutic intervention.

L14 ANSWER 5 OF 15 MEDLINE on STN DUPLICATE 3

2006581555. PubMed ID: 16858684. Peptabody-EGF: a novel apoptosis inducer targeting ErbB1 receptor overexpressing cancer cells. Fattah Omar M; Cloutier Sylvain M; Kundig Christoph; Felber Loyse M; Gygi Christian M; Jichlinski Patrice; Leisinger Hans-Jurg; Gauthier Eric R; Mach Jean Pierre; Deperthes David. (Department of Urology, Urology Research Unit, CHUV, Epalinges, Switzerland.) International journal of cancer. Journal international du cancer, (2006 Nov 15) Vol. 119, No. 10, pp. 2455-63. Journal code: 0042124. ISSN: 0020-7136. Pub. country: United States. Language: English.

AB The epidermal growth factor receptor (EGFR) plays a central role in cell life by controlling processes such as growth or proliferation. This receptor is commonly overexpressed in a number of epithelial malignancies and its upregulation is often associated with an aggressive phenotype of the tumor. Thus, targeting of EGFR represents a very promising challenge in oncology, and antibodies raised against this receptor have been investigated as potential antitumor agents. Various putative mechanisms of action were proposed for such antibodies, including decreased proliferation, induction of apoptosis, stimulation of the immunological response against targeted cancer cells or combinations thereof. We report here the development of an alternative high affinity molecule that is directed against EGFR. Production of this pentameric protein, named peptabody-EGF, includes expression in a bacterial expression system and subsequent refolding and multimerization of peptabody monomers. The protein complex contains 5 human EGF ligand domains, which confer specific binding towards the extracellular portion of EGFR. Receptor binding of the peptabody-EGF had a strong antiproliferative effect on different cancer cell lines overexpressing EGFR. However, cells expressing constitutive levels of the target receptor were barely affected. Peptabody-EGF treated cancer cells exhibited typical characteristics of apoptosis, which was found to be induced within 30 min after the addition of the peptabody-EGF. In vitro experiments demonstrated a significantly higher binding activity for peptabody-EGF than for the therapeutic monoclonal EGFR antibody Mab-425. Furthermore, the antitumor action provoked by the peptabody-EGF was greatly superior than antibody mediated effects when tested on EGFR overexpressing cancer cell lines. These findings suggest a potential application of this high affinity molecule as a novel tool for anti-EGFR therapy.

L14 ANSWER 6 OF 15 EMBASE

2006266133 EMBASE EGF receptor mutations in lung cancer: From humans to mice and maybe back to humans. Arteaga C.L.. C.L. Arteaga, Departments of

Medicine and Cancer Biology, Breast Cancer Research Program, Vanderbilt-Ingram Comprehensive Cancer Center, Nashville, TN 37232, United States. carlos.arteaga@vanderbilt.edu. Cancer Cell Vol. 9, No. 6, pp. 421-423 13 Jun 2006.
Refs: 23.
ISSN: 1535-6108. CODEN: CCAECI
S 1535-6108(06)00151-6. Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20060706. Last Updated on STN: 20060706

AB Deletions in exon 19 and nucleotide substitutions in exon 21 are the most common mutations of the EGFR (ErbB1) in NSCLC. These mutations endow the receptor with constitutive kinase activity. Most tumors expressing these mutants respond well to EGFR tyrosine kinase inhibitors, suggesting that they are dependent on mutant EGFR signaling. Two groups developed transgenic mice in which expression of these mutants is temporally induced in mouse lung. Mice expressing EGFR mutants develop bronchioloalveolar cancer and lung adenocarcinoma, which are highly sensitive to EGFR inhibitors. These mouse models provide important opportunities for studying the biology of NSCLC and the refinement of anti-EGFR therapies.

L14 ANSWER 7 OF 15 EMBASE

2006374473 EMBASE The complexity of targeting EGFR signalling in cancer: From expression to turnover. Sebastian S.; Settleman J.; Reshkin S.J.; Azzariti A.; Bellizzi A.; Paradiso A.. A. Paradiso, Clinical Experimental Oncology Laboratory, National Cancer Institute, Via Amendola, 209, 70126 Bari, Italy. a.paradiso@oncologico.bari.it. Biochimica et Biophysica Acta - Reviews on Cancer Vol. 1766, No. 1, pp. 120-139 2006.
Refs: 250.
ISSN: 0304-419X. CODEN: BBACEU
S 0304-419X(06)00032-1. Pub. Country: Netherlands. Language: English. Summary Language: English.
Entered STN: 20060824. Last Updated on STN: 20060824

AB The epidermal growth factor receptor (ErbB1 or EGFR) has been found to be altered in a variety of human cancers. A number of agents targeting these receptors, including specific antibodies directed against the ligand-binding domain of the receptor and small molecules that inhibit kinase activity are either in clinical trials or are already approved for clinical treatment. However, identifying patients that are likely to respond to such treatments has been challenging. As a consequence, it still remains important to identify additional alterations of the tumor cell that contribute to the response to EGFR-targeted agents. While EGFR-mediated signalling pathways have been well established, there is still a rather limited understanding of how intracellular protein-protein interactions, ubiquitination, endocytosis and subsequent degradation of EGFR contribute to the determination of sensitivity to EGFR targeting agents and are emerging areas of investigation. This review primarily focuses on the basic signal transduction pathways mediated through activated membrane bound and/or endosomal EGFR and emphasizes the need to co-target additional proteins that function either upstream or downstream of EGFR to improve cancer therapy.

L14 ANSWER 8 OF 15 SCISEARCH

2005:579387 The Genuine Article (R) Number: 930JI. Clinical applications for targeted therapy in bladder cancer. Adam L; Kassouf W; Dinney C P N (Reprint). Univ Texas, MD Anderson Canc Ctr, Dept Urol, 1515 Holcombe Blvd, Unit 1373, Houston, TX 77030 USA (Reprint); Univ Texas, MD Anderson

Canc Ctr, Dept Urol, Houston, TX 77030 USA; Univ Texas, MD Anderson Canc Ctr, Dept Canc Biol, Houston, TX 77030 USA. cdinney@mdanderson.org.
UROLOGIC CLINICS OF NORTH AMERICA (MAY 2005) Vol. 32, No. 2, pp. 239-+. ISSN: 0094-0143. Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399 USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Transitional cell carcinoma (TCC) of the bladder is the fourth most common solid-tumor malignancy in men in the United States. Approximately 17,060 men in the United States died from TCC of the bladder in 2004; most of the deaths were due to metastatic disease [1]. Metastatic TCC is usually treated with systemic chemotherapy, including regimens such as M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin) (2-4]. However, despite systemic chemotherapy with even the most effective regimens, most patients with distant metastatic bladder cancer die of the disease after a median survival duration of 18 months [3,4]. Although considerable efforts have been made to escalate the dose of MNAC, to modulate the components of the regimens, and to use novel combination regimens that include active agents such as paclitaxel, gemcitabine, and ifosfamide, there has been no improvement in survival [5-10]. Although some of these newer regimens produce fewer toxic side effects than MNAC, there is yet no compelling evidence that they improve patient survival. In general, the treatment of metastatic TCC of the bladder by classic cytotoxic chemotherapy has reached a therapeutic plateau. Despite high rates of response to treatment, the disease is generally incurable. However, it is clear that cytotoxic chemotherapy has provided significant palliation for many patients, and has resulted in improved outcome, probability for cure, or both in the adjuvant setting of microscopic metastatic disease.

Although chemotherapy is still an important component of combined therapy, the need for more effective treatment options exists. Fortunately, an improved understanding of the biology of malignancy is finally facilitating the design of novel therapeutic approaches to battle cancer. Urothelial transformation involves several cellular events including the deregulation of cellcycle and apoptotic pathways via mutation or altered expression of p53, p21/WAF-1, pRB, p27, and INK4A (p16). Progression of urothelial carcinoma has also been related to various members of the erbB family, vascular epidermal growth factor (VEGF), nerve factor-kappa B (NF kappa B), Akt, PTEN, and cyclooxygenase/2 (COX-2) [11]. All of these molecules are potential targets for novel therapies. The focus of this article is the aberrant signal transduction of members of the erbB family (ie, epidermal growth factor receptor [EGFR], and human epidermal growth factor receptors [HER]-2, -3, and -4) in TCC of the bladder. EGFR was sequenced and cloned by Ullrich in 1984 [12]. EGFR, HER1, or c-erbB1, is the prototype of the type I receptor tyrosine kinase (RTK) family, which also includes HER2 (cerbB2), HER3 (c-erbB-3), and HER4 (c-erbB-4) [13-15]. EGFR family members transmit the biologic effects of the EGF family of ligands, which includes EGF, transforming growth factor-alpha (TGF alpha), amphiregulin, heparin-binding (HB)-EGF, betacellulin, and epiregulin. Ligand binding induces the formation of homodimers or heterodimers between EGFR and other members of this family, autophosphorylation of tyrosine residues in its intracellular domain, and activation of downstream signaling pathways [13-15]. These phosphotyrosines, in turn, phosphorylate other intracellular proteins that contain src homologous domains (SH2 and SH3), such as ras-associated GTPase activating protein, phosphatidylinositol3-kinase, and phospholipase C gamma. The downstream signaling pathways activated by these intracellular proteins include the ras/raf MAPKinase, phosphatidylinositol-3-kinase, and protein kinase C pathways, which ultimately lead to increased nuclear transcription and subsequent cellular proliferation [15,16]. Overexpression of EGFR alone or accompanied by

production of one or more of its ligands, such as TGF alpha, has been reported in a range of human malignancies and is often associated with poor prognosis [16,17]. Overexpression of EGFR in bladder cancer has been widely reported [1823]. The reports suggest the presence of erbB1 in 23% to 100% of TCC samples. Several studies have shown that EGFR is positively associated with advanced tumor stage, tumor progression, and poor clinical outcome [24]. Immunohistochemical analyses suggest that rather than actual overexpression of erbB1 in TCC is the actual change in the distribution of the molecule, from basal layer in normal urothelium to all layers in premalignant or malignant urotheliums [25,26]. Other studies have demonstrated that expression of erbB1 and of erbB2 is downregulated in TCC compared with the expression in normal urothelium [27]. Still other studies have demonstrated erbB3 in 20% to 56% and erbB4 in 11% to 30% of cases of TCC, but reduced expression of erbB3 and erbB4 in TCC compared with normal tissues [27]. Statistical analyses of erbB expression patterns and clinical parameters have resulted in varying conclusions about the prognostic significance of erbB expression in TCC [27-32].

However, in patients with muscle-invasive TCC of the bladder, a retrospective immunohistochemical study has shown erbB2 overexpression to be a independent predictor of reduced cancer-specific survival [33]. In contrast, another prospective study found that erbB2 overexpression in the context of paclitaxel-based chemotherapy significantly decreased the risk of death [34]. On the basis of discovery of variant isoforms of the erbB family members, a series of studies was initiated that focused on acquiring quantitative information about erbB status, which was considered critical for selecting patients for erbB inhibitor therapies, and for evaluating the potential use of erbBs as prognostic indicators for patients with cancer. A report by Juntilla et al [35] describing specific erbB4 cytoplasmic or juxtamembrane isoforms overexpressed in TCC compared with its expression in interstitial cystitis or normal bladder, is an example of such finding. Thus, preclinical evidence about the expression levels of specific erbBs in TCC tissues, although controversial at the moment, may be verified through a more refined investigation. Several erbB I variants, somatic mutations, deletions, or truncations have been described for erbB1 in epithelial cancers, including lung, colon, and breast cancers [36-39]. For example, the erbBvIII variant, which lacks the extracellular domain, has been shown to be specifically expressed in tumor tissues rather than in normal, adjacent tissues and to activate aberrant signaling pathways relevant for EGFR-targeted therapy [40,41]. However, there currently are no studies investigating this aspect in bladder cancer.

L14 ANSWER 9 OF 15 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

2005:387361 The Genuine Article (R) Number: 912JF. Characterization of HER1 (c-erbB1) status in locally advanced breast cancer using fluorescence in situ hybridization and immunohistochemistry. Corzo C (Reprint); Tusquets I; Salido M; Corominas J M; Bellet M; Suarez M; Baro T; Fabregat X; Serrano S; Sole F. Hosp del Mar, IMAS, Unitat Rec Translac Tumors Solids, Serv Patol, Lab Citogenet & Biol Mol, Pg Maritim 25-29, ES-08003 Barcelona, Spain (Reprint); Hosp del Mar, IMAS, Unitat Rec Translac Tumors Solids, Serv Patol, Lab Citogenet & Biol Mol, ES-08003 Barcelona, Spain; Hosp del Mar, IMAS, Unitat Rec Translac Tumors Solids, Med Oncol Serv, ES-08003 Barcelona, Spain; Univ Autonoma Barcelona, Dept Biol Cellular Fisiol & Immunol, E-08193 Barcelona, Spain. E0062@imas.imim.es. TUMOR BIOLOGY (2005) Vol. 26, No. 1, pp. 25-30. ISSN: 1010-4283. Publisher: KARGER, ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Epidermal growth factor receptor (EGFR) is a 170-kDa

transmembrane glycoprotein encoded by the HER1 protooncogene, located at 7p12. This receptor is related to the pathogenesis of breast cancer. The aim of this study was to analyze the status of HER1 using fluorescence in situ hybridization (FISH) and immunohistochemistry in a series of 48 patients with locally advanced breast cancer (LABC). Before neoadjuvant chemotherapy, core biopsies were taken from patients with LABC and were processed into paraffin blocks. Biopsies were then studied using FISH with a HER1 probe (Vysis, Downers Grove, Ill., USA). They were also analyzed immunohistochemically using two different EGFR antibodies from DakoCytomation (Denmark, A/S) and from Zymed (San Francisco, Calif., USA). HER1 amplifications were not found, although 31% of the cases presented aneusomy of chromosome 7. Only 2 cases presented EGFR expression. LABC presented a low level of EGFR expression. HER1 amplification was not present in LABC, although the polysomy of chromosome 7 was a common finding. Copyright (C) 2005 S. Karger AG, Basel.

L14 ANSWER 10 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
2004:404840 Document No. 142:129837 Anti-EGFR-mediated radiosensitization as a result of augmented EGFR expression.
Bonner, James A.; Buchsbaum, Donald J.; Russo, Suzanne M.; Fiveash, John B.; Trummell, Hoa Q.; Curiel, David T.; Raisch, Kevin P. (Department of Radiation Oncology, Univ. Alabama Sch Med., Birmingham, AL, USA).
International Journal of Radiation Oncology, Biology, Physics, 59(2, Suppl.), 2-10 (English) 2004. CODEN: IOBPD3. ISSN: 0360-3016.
Publisher: Elsevier Science Inc..
AB Elevated epidermal growth factor receptor (EGFR) expression has correlated with a poor prognosis after standard treatment of several malignancies. However, it is not clear whether the absolute level of EGFR expression affects the radiosensitizing properties of anti-EGFR treatments. A better understanding of this question would be helpful for the design of protocols that deliver these treatments. To explore this question, cells (LS174T) that did not display inherent anti-EGFR treatment-induced radiosensitization were selected for studies that could potentially enhance EGFR expression. Human colon carcinoma cells (LS174T), which did not show radiosensitization by anti-EGFR treatments, were employed for these studies. (Also, these cells were not responsive to the antiproliferative effects of anti-EGFR treatment.). Using standard transfection techniques (eukaryotic expression vector) as well as an adenoviral construct to enhance EGFR expression, LS174T cells were transduced in a manner that resulted in enhanced expression of EGFR. Subsequently, standard proliferation studies were performed to test the radiosensitizing properties of anti-EGFR treatment (an anti-EGFR monoclonal antibody: IMC-C225). Studies were undertaken to stably transfect LS174T cells with EGFR. The stable transfectants, LS174T.EGFR cells, were responsive to the antiproliferative effects of anti-EGFR treatment, in contrast to the parent LS174T cells. Similar results were demonstrated when the cells were infected with AdEGFR. Addnl., the LS174T.EGFR cells were responsive to the radiosensitizing properties of anti-EGFR treatment (IMC-C225), whereas the parent cells were not. Although the level of EGFR expression is of prognostic significance in many tumor models, the response of cells to anti-EGFR treatment alone, or combinations of this treatment with radiation or chemotherapy, depends upon many factors that are not necessarily related to the inherent EGFR expression of the tumor cells. However, the studies reported herein, demonstrate that when LS174T cells were transduced to show increased EGFR expression, they became responsive to the radiosensitizing properties of anti-EGFR treatments.

L14 ANSWER 11 OF 15 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2003257887 EMBASE Gene products involved in metastasis of bladder cancer. Davies B.R.. Dr. B.R. Davies, Schl. of Surg. and Reproductive Sci., University of Newcastle, Medical School, Newcastle-Upon-Tyne NE2 4HH, United Kingdom. B.R.Davies@ncl.ac.uk. Histology and Histopathology Vol. 18, No. 3, pp. 969-980 2003.
Refs: 104.
ISSN: 0213-3911. CODEN: HIHIES
Pub. Country: Spain. Language: English. Summary Language: English.
Entered STN: 20030717. Last Updated on STN: 20030717

AB Metastasis is usually responsible for mortality in patients suffering from muscle invasive bladder cancer. Whilst expression of a great number of genes and their protein products have been associated with metastasis and/or poor prognosis in bladder cancer, evidence that they actively drive the metastatic process, and hence make potentially good therapeutic targets, is often lacking. This is due to the limited number and application of effective animal models which reflect the pathogenesis of the human disease. In this review I will discuss the processes involved in metastasis, consider the established animal models of bladder cancer progression and metastasis, and review the evidence for a role of various gene products in this process. Consideration of clinical studies in conjunction with evidence from experimental animal models reveals that the tyrosine kinase receptor erbB1/EGFR, the calcium binding protein S100A4 and the the cell cycle arrest/apoptosis-inducing p53 protein are amongst the most promising targets for therapy against metastatic disease in patients with bladder cancer.

L14 ANSWER 12 OF 15 MEDLINE on STN DUPLICATE 4

2003134501. PubMed ID: 12648471. ErbB-targeted therapeutic approaches in human cancer. Arteaga Carlos L. (Department of Medicine, Vanderbilt University School of Medicine, and Breast Cancer Program, Vanderbilt-Ingram Comprehensive Cancer Center, Nashville, TN 37232, USA.. arlos.artega@vanderbilt.edu) . Experimental cell research, (2003 Mar 10) Vol. 284, No. 1, pp. 122-30. Ref: 100. Journal code: 0373226. ISSN: 0014-4827. Pub. country: United States. Language: English.

AB The overexpression and aberrant function of the epidermal growth factor receptor (EGFR, erbB1, HER1) and its ligands and coreceptors in a wide spectrum of epithelial cancers have provided a rationale for targeting this signaling network with novel treatment approaches. Several antireceptor therapeutic strategies have been pursued, but two stand ahead in their clinical development. One approach has been the generation of small molecules that compete with adenosine triphosphate (ATP) for binding to the receptor's kinase pocket, thus blocking receptor activation and the transduction of postreceptor signals. The second approach utilizes humanized monoclonal antibodies generated against the receptor's ligand-binding extracellular domain. These antibodies block binding of receptor-activating ligands and, in some cases, can induce receptor endocytosis and downregulation. Clinical studies already suggest that both of these approaches, either alone or in combination with standard anticancer therapies, are well tolerated and can induce clinical responses and tumor stabilization in a variety of common carcinomas.

L14 ANSWER 13 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

2003:143026 Document No. 139:209971 Combination of epidermal growth factor receptor targeted therapy with radiation therapy for malignant gliomas. Krishnan, Sunil; Rao, Ravi D.; James, C. David; Sarkaria, Jann N. (Department of Oncology, Mayo Clinic and Foundation, Rochester, MN, USA). Frontiers in Bioscience, 8, E1-E13 (English) 2003. CODEN: FRBIF6. ISSN: 1093-4715. URL: http://WWW.bioscience.org/2003/v8/e/895/pdf.pdf Publisher: Frontiers in Bioscience.

AB A review. Glioblastoma multiform (GBM) are extremely aggressive brain tumors characterized by resistance to standard treatment modalities including surgery, radiation therapy and chemotherapy. While radiation therapy is the standard treatment after surgical resection, these tumors invariably recur and are associated with a uniformly dismal prognosis. Cytotoxic chemotherapy has failed to improve on the modest gains conferred by radiation therapy. Our understanding of the mol. events driving glioma-genesis has led to the recognition of frequent alterations in the epidermal growth factor receptor (EGFR) pathway, leading to increased aggressiveness and a poorer prognosis. Based on the importance of EGFR in the development of malignancy in multiple tumor types, several classes of novel therapeutic agents have been developed that specifically target EGFR. This review outlines the relevance of normal and aberrant EGFR signaling in the biol. of gliomas, the strategies for inhibiting EGFR activity and the rationale for combining EGFR inhibitors with radiation therapy in the treatment of GBM.

L14 ANSWER 14 OF 15 MEDLINE on STN DUPLICATE 5
2002046609. PubMed ID: 11751413. Epidermal growth factor receptor (HER1) tyrosine kinase inhibitor ZD1839 (Iressa) inhibits HER2/neu (erbB2)-overexpressing breast cancer cells in vitro and in vivo. Moulder S L; Yakes F M; Muthuswamy S K; Bianco R; Simpson J F; Arteaga C L. (Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee 37232-6307, USA.) Cancer research, (2001 Dec 15) Vol. 61, No. 24, pp. 8887-95. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.
AB Aberrrant signaling by the epidermal growth factor receptor [EGFR (HER1, erbB1)] and/or HER2/neu tyrosine kinases is present in a cohort of breast carcinomas. Because HER2 is constitutively phosphorylated in some breast tumors, we speculated that, in these cancers, transmodulation of HER2 may occur via EGFR signaling. To test this possibility, we examined the effect of EGFR -specific kinase inhibitors against the HER2-overexpressing human breast tumor lines BT-474, SKBR-3, MDA-361, and MDA-453. ZD1839 (Iressa) is an ATP-mimetic that inhibits the purified EGFR and HER2 kinases in vitro with an IC(50) of 0.033 and >3.7 microM, respectively. The specificity of ZD1839 against EGFR was confirmed in Rat1 fibroblasts transfected with EGFR or HER2 chimeric receptors activated by synthetic ligands without the interference of endogenous receptors. Treatment of all breast cancer cell lines (except MDA-453) with 1 microM ZD1839 almost completely eliminated HER2 phosphorylation. In contrast, the incorporation of [gamma-(32)P]ATP in vitro onto HER2 receptors isolated from BT-474 cells was unaffected by 1 microM ZD1839. EGFR is expressed by BT-474, SKBR-3, and MDA-361 but not by MDA-453 cells, suggesting that ZD1839-mediated inhibition of the EGFR kinase explained the inhibition of HER2 phosphorylation in vivo. In SKBR-3 cells, ZD1839 exhibited a greater growth-inhibitory effect than Herceptin, a monoclonal antibody against the HER2 ectodomain. In both SKBR-3 and BT-474 cells, treatment with ZD1839 plus Herceptin induced a greater apoptotic effect than either inhibitor alone. Finally, ZD1839 completely prevented growth of BT-474 xenografts established in nude mice and enhanced the antitumor effect of Herceptin. These data imply that EGFR tyrosine kinase inhibitors will be effective against HER2-overexpressing breast tumor cells that also express EGFR and support their use in combination with HER2 antibodies, such as Herceptin, against mammary carcinomas with high levels of the HER2 proto-oncogene.

L14 ANSWER 15 OF 15 MEDLINE on STN DUPLICATE 6
2001098135. PubMed ID: 11156523. Molecular mechanisms underlying ErbB2/HER2 action in breast cancer. Harari D; Yarden Y. (Department of Biological Regulation, the Weizmann Institute of Science, Rehovot, Israel.

) Oncogene, (2000 Dec 11) Vol. 19, No. 53, pp. 6102-14. Ref: 198. Journal code: 8711562. ISSN: 0950-9232. Pub. country: England: United Kingdom. Language: English.

AB Overexpression of ErbB2, a receptor-like tyrosine kinase, is shared by several types of human carcinomas. In breast tumors the extent of overexpression has a prognostic value, thus identifying the oncoprotein as a target for therapeutic strategies. Already, antibodies to ErbB2 are used in combination with chemotherapy in the treatment of metastasizing breast cancer. The mechanisms underlying the oncogenic action of ErbB2 involve a complex network in which ErbB2 acts as a ligand-less signaling subunit of three other receptors that directly bind a large repertoire of stroma-derived growth factors. The major partners of ErbB2 in carcinomas are ErbB1 (also called EGFR) and ErbB3, a kinase-defective receptor whose potent mitogenic action is activated in the context of heterodimeric complexes. Why ErbB2-containing heterodimers are relatively oncopotent is a function of a number of processes. Apparently, these heterodimers evade normal inactivation processes, by decreasing the rate of ligand dissociation, internalizing relatively slowly and avoiding the degradative pathway by returning to the cell surface. On the other hand, the heterodimers strongly recruit survival and mitogenic pathways such as the mitogen-activated protein kinases and the phosphatidylinositol 3-kinase. Hyper-activated signaling through the ErbB-signaling network results in dysregulation of the cell cycle homeostatic machinery, with upregulation of active cyclin-D/CDK complexes. Recent data indicate that cell cycle regulators are also linked to chemoresistance in ErbB2-dependent breast carcinoma. Together with D-type cyclins, it seems that the CDK inhibitor p21waf1 plays an important role in evasion from apoptosis. These recent findings herald a preliminary understanding of the output layer which connects elevated ErbB-signaling to oncogenesis and chemoresistance.

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L15 ANSWER 1 OF 1 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006500693 EMBASE Peptabody-EGF: A novel apoptosis inducer targeting ErbB1 receptor overexpressing cancer cells. Fattah O.M.; Cloutier S.M.; Kundig C.; Felber L.M.; Gygi C.M.; Jichlinski P.; Leisinger H.-J.; Gauthier E.R.; Mach J.P.; Deperthes D.. D. Deperthes, Urology Research Unit/Med Discovery S.A., Biopole, Ch. Croisettes 22, CH-1066 Epalinges, Switzerland. david.deperthes@med-discovery.com. International Journal of Cancer Vol. 119, No. 10, pp. 2455-2463 15 Nov 2006.
Refs: 29.
ISSN: 0020-7136. E-ISSN: 1097-0215. CODEN: IJCNAW
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20061027. Last Updated on STN: 20061027

AB The epidermal growth factor receptor (EGFR) plays a central role in cell life by controlling processes such as growth or proliferation. This receptor is commonly overexpressed in a number of epithelial malignancies and its upregulation is often associated with an aggressive phenotype of the tumor. Thus, targeting of EGFR represents a very promising challenge in oncology, and antibodies raised against this receptor have been investigated as potential antitumor agents. Various putative mechanisms of action were proposed for such antibodies, including decreased proliferation, induction of apoptosis, stimulation of the immunological response against targeted cancer cells or combinations thereof. We report here the development of an alternative high affinity molecule that is directed against

EGFR. Production of this pentameric protein, named peptabody-EGF, includes expression in a bacterial expression system and subsequent refolding and multimerization of peptabody monomers. The protein complex contains 5 human EGF ligand domains, which confer specific binding towards the extracellular portion of EGFR. Receptor binding of the peptabody-EGF had a strong antiproliferative effect on different cancer cell lines overexpressing EGFR. However, cells expressing constitutive levels of the target receptor were barely affected. Peptabody-EGF treated cancer cells exhibited typical characteristics of apoptosis, which was found to be induced within 30 min after the addition of the peptabody-EGF. In vitro experiments demonstrated a significantly higher binding activity for peptabody-EGF than for the therapeutic monoclonal EGFR antibody Mab-425. Furthermore, the antitumor action provoked by the peptabody-EGF was greatly superior than antibody mediated effects when tested on EGFR overexpressing cancer cell lines. These findings suggest a potential application of this high affinity molecule as a novel tool for anti-EGFR therapy. .COPYRGT. 2006 Wiley-Liss, Inc.

=> s l11 and "MAb 425"
L16 7 L11 AND "MAB 425"

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L17 3 DUP REMOVE L16 (4 DUPLICATES REMOVED)

=> d l17 1-3 cbib abs

L17 ANSWER 1 OF 3 MEDLINE on STN DUPLICATE 1
2006581555. PubMed ID: 16858684. Peptabody-EGF: a novel apoptosis inducer targeting ErbB1 receptor overexpressing cancer cells. Fattah Omar M; Cloutier Sylvain M; Kundig Christoph; Felber Loyse M; Gygi Christian M; Jichlinski Patrice; Leisinger Hans-Jurg; Gauthier Eric R; Mach Jean Pierre; Deperthes David. (Department of Urology, Urology Research Unit, CHUV, Epalinges, Switzerland.) International journal of cancer. Journal international du cancer, (2006 Nov 15) Vol. 119, No. 10, pp. 2455-63. Journal code: 0042124. ISSN: 0020-7136. Pub. country: United States. Language: English.

AB The epidermal growth factor receptor (EGFR) plays a central role in cell life by controlling processes such as growth or proliferation. This receptor is commonly overexpressed in a number of epithelial malignancies and its upregulation is often associated with an aggressive phenotype of the tumor. Thus, targeting of EGFR represents a very promising challenge in oncology, and antibodies raised against this receptor have been investigated as potential antitumor agents. Various putative mechanisms of action were proposed for such antibodies, including decreased proliferation, induction of apoptosis, stimulation of the immunological response against targeted cancer cells or combinations thereof. We report here the development of an alternative high affinity molecule that is directed against EGFR. Production of this pentameric protein, named peptabody-EGF, includes expression in a bacterial expression system and subsequent refolding and multimerization of peptabody monomers. The protein complex contains 5 human EGF ligand domains, which confer specific binding towards the extracellular portion of EGFR. Receptor binding of the peptabody-EGF had a strong antiproliferative effect on different cancer cell lines overexpressing EGFR. However, cells expressing constitutive levels of the target receptor were barely affected. Peptabody-EGF treated cancer cells exhibited typical characteristics of apoptosis, which was found to be induced within 30 min after the addition of the peptabody-EGF. In vitro experiments demonstrated a significantly higher binding activity for

peptabody-EGF than for the therapeutic monoclonal EGFR antibody Mab-425. Furthermore, the antitumor action provoked by the peptabody-EGF was greatly superior than antibody mediated effects when tested on EGFR overexpressing cancer cell lines. These findings suggest a potential application of this high affinity molecule as a novel tool for anti-EGFR therapy.

L17 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
2004:333597 Document No. 140:344924 Bispecific anti-ErbB antibodies and their use in tumor therapy. Kreysch, Hans-Georg (Merck Patent GmbH, Germany). PCT Int. Appl. WO 2004032961 A1 20040422, 52 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-EP11165 20031009. PRIORITY: EP 2002-22389 20021010; EP 2002-22390 20021010.
AB The invention relates to novel bispecific antibodies and their use in tumor therapy. The novel antibodies have the ability to bind to ErbB receptors, preferably ErbB1 receptors, which are overexpressed on many cancer tissues. Since the different specificities of the antigen-binding sites are directed to different epitopes within the binding domain of same or different ErbB receptors, these antibodies are more effective with respect to inhibition and down-regulation of the ErbB receptor and the corresponding signaling cascade. For example, preparation of F(ab')2 fragments of humanized monoclonal antibodies MAb 425 and chimeric MAb 225 was presented.

L17 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
2004:333596 Document No. 140:344923 Pharmaceutical compositions directed to ErbB-1 receptors. Kreysch, Hans-Georg; Schmidt, Juergen (Merck Patent GmbH, Germany). PCT Int. Appl. WO 2004032960 A1 20040422, 57 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-EP11164 20031009. PRIORITY: EP 2002-22390 20021010; EP 2002-22389 20021010.
AB The invention relates to pharmaceutical compns. comprising different mols., preferably monoclonal antibodies (MAbs), each comprising epitopes that bind simultaneously to different sites within the same ErbB-1 receptor domain. The preferred antibodies according to this invention are MAb 425 and MAb 225 each in its murine, chimeric and humanized version. The invention relates to the use and methods for an improved treatment of preferably tumors by means of said compns. For example, an effector-target cell aggregation as prerequisite for antibody-dependent cell-mediated cytotoxicity was investigated using EGFR pos. A431 target cells and two antibodies with specificity for different epitopes of the human EGFR (Cetuximab and EMD 72000). The maximum percentage of aggregates was increased in samples incubated with a mixture of both MAbs at a lower total protein concentration

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=> s (kreysch h?/au or schmidt j?/au)
L18      16660 (KREYSCH H?/AU OR SCHMIDT J?/AU)

=> s l18 and anti-EGFR1
L19          0 L18 AND ANTI-EGFR1

=> s l18 and ErbB1 antibody
L20          0 L18 AND ERBB1 ANTIBODY

=> s l18 and antibod?
L21        586 L18 AND ANTIBOD?

=> s l21 and EGFR
L22          3 L21 AND EGFR

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L23           3 DUP REMOVE L22 (0 DUPLICATES REMOVED)

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L23  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2007 ACS on STN
2004:333596   Document No. 140:344923  Pharmaceutical compositions directed to
     ErbB-1 receptors.  Kreysch, Hans-Georg; Schmidt, Juergen
     (Merck Patent GmbH, Germany).  PCT Int. Appl. WO 2004032960 A1 20040422,
     57 pp.  DESIGNATED STATES: W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR,
     BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB,
     GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
     LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG,
     PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ,
     UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH,
     CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE,
     NL, PT, SE, SN, TD, TG, TR.  (English).  CODEN: PIXXD2.  APPLICATION: WO
     2003-EP11164 20031009.  PRIORITY: EP 2002-22390 20021010; EP 2002-22389
     20021010.
AB   The invention relates to pharmaceutical compns. comprising different
     mols., preferably monoclonal antibodies (MAbs), each comprising
     epitopes that bind simultaneously to different sites within the same
     ErbB-1 receptor domain.  The preferred antibodies according to
     this invention are MAb 425 and MAb 225 each in its murine, chimeric and
     humanized version.  The invention relates to the use and methods for an
     improved treatment of preferably tumors by means of said compns.  For
     example, an effector-target cell aggregation as prerequisite for
     antibody-dependent cell-mediated cytotoxicity was investigated
     using EGFR pos. A431 target cells and two antibodies
     with specificity for different epitopes of the human EGFR
     (Cetuximab and EMD 72000).  The maximum percentage of aggregates was
     increased in samples incubated with a mixture of both MAbs at a lower total
     protein concentration

L23  ANSWER 2 OF 3  BIOSIS  COPYRIGHT (c) 2007 The Thomson Corporation  on STN
2003:502686  Document No.: PREV200300498451. The humanized monoclonal anti-
     EGFR antibody EMD72000 potently inhibits the growth of
     EGFR-expressing human tumor xenografts insensitive to
     chemotherapeutic drugs. Burger, Angelika M. [Reprint Author]; Heiss, Nina
     S.; Kreysch, Hans-Georg; Schandelmaier, Kathrin; Wirth, Gregory;
     Fiebig, Heinz H.; Grell, Matthias. Oncotest, Freiburg, Germany.
     Proceedings of the American Association for Cancer Research Annual
     Meeting, (July 2003) Vol. 44, pp. 1139. print.
     Meeting Info.: 94th Annual Meeting of the American Association for Cancer
     Research. Washington, DC, USA. July 11-14, 2003.
     ISSN: 0197-016X. Language: English.
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L23 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
2002:539555 Document No. 137:108304 Pharmaceutical compositions comprising Receptor tyrosine kinase-inhibiting antibodies and angiogenesis inhibitors for treating cancer and metastasis. Goodman, Simon; Kreysch, Hans-Georg (Merck Patent Gmbh, Germany). PCT Int. Appl. WO 2002055106 A2 20020718, 45 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-EP15241 20011221. PRIORITY: EP 2001-100507 20010109.

AB The invention relates to a combination therapy for the treatment of tumors and tumor metastases comprising administration of receptor tyrosine kinase antagonists/inhibitors, especially ErbB receptor antagonists, more preferably EGF receptor (Her 1) antagonists and anti-angiogenic agents, preferably integrin antagonists, optionally together with agents or therapy forms that have additive or synergistic efficacy when administered together with said combination of antagonists/inhibitors, such as chemotherapeutic agents and or radiation therapy. The therapy can result in a synergistic potential increase of the inhibition effect of each individual therapeutic on tumor cell proliferation, yielding more effective treatment than found by administering an individual component alone.

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L24 2 L21 AND ERBB1

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L25 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
2004:333597 Document No. 140:344924 Bispecific anti-ErbB antibodies and their use in tumor therapy. Kreysch, Hans-Georg (Merck Patent GmbH, Germany). PCT Int. Appl. WO 2004032961 A1 20040422, 52 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-EP11165 20031009. PRIORITY: EP 2002-22389 20021010; EP 2002-22390 20021010.

AB The invention relates to novel bispecific antibodies and their use in tumor therapy. The novel antibodies have the ability to bind to ErbB receptors, preferably ErbB1 receptors, which are overexpressed on many cancer tissues. Since the different specificities of the antigen-binding sites are directed to different epitopes within the binding domain of same or different ErbB receptors, these antibodies are more effective with respect to inhibition and down-regulation of the ErbB receptor and the corresponding signaling cascade. For example, preparation of F(ab')2 fragments of humanized monoclonal antibodies MAb 425 and chimeric MAb 225 was presented.

L25 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
2004:333596 Document No. 140:344923 Pharmaceutical compositions directed to ErbB-1 receptors. Kreysch, Hans-Georg; Schmidt, Juergen (Merck Patent GmbH, Germany). PCT Int. Appl. WO 2004032960 A1 20040422, 57 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-EP11164 20031009. PRIORITY: EP 2002-22390 20021010; EP 2002-22389 20021010.

AB The invention relates to pharmaceutical compns. comprising different mols., preferably monoclonal antibodies (MAbs), each comprising epitopes that bind simultaneously to different sites within the same ErbB-1 receptor domain. The preferred antibodies according to this invention are MAb 425 and MAb 225 each in its murine, chimeric and humanized version. The invention relates to the use and methods for an improved treatment of preferably tumors by means of said compns. For example, an effector-target cell aggregation as prerequisite for antibody-dependent cell-mediated cytotoxicity was investigated using EGFR pos. A431 target cells and two antibodies with specificity for different epitopes of the human EGFR (Cetuximab and EMD 72000). The maximum percentage of aggregates was increased in samples incubated with a mixture of both MAbs at a lower total protein concentration

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L26 17 L21 AND COMBINATION

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L27 ANSWER 1 OF 14 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
2007060458 EMBASE Four Cases of Sirolimus-Associated Interstitial Pneumonitis: Identification of Risk Factors. Morath C.; Schwenger V.; Ksoll-Rudek D.; Sommerer C.; Beimler J.; Schmidt J.; Zeier M..
C. Morath, Department of Nephrology, University of Heidelberg, Heidelberg, Germany. christian_morath@med.uni-heidelberg.de. Transplantation Proceedings Vol. 39, No. 1, pp. 99-102 2007.
Refs: 21.
ISSN: 0041-1345. CODEN: TRPPA8
S 0041-1345(06)01482-5. Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20070319. Last Updated on STN: 20070319

AB Sirolimus-associated interstitial pneumonitis is a severe side effect of sirolimus therapy; fatal outcomes have been described. We report 4 patients with sirolimus-associated interstitial pneumonitis and review the literature for risk factors for the development of disease. Until June 2005, 48 patients received either de novo sirolimus treatment (n = 7) or were switched from a calcineurin inhibitor-containing regimen to a sirolimus-based protocol for various indications (n = 41). Compared with the 44 patients on sirolimus therapy with no evidence of a disorder, the 4 patients (8.3%) who developed suspected sirolimus-associated interstitial pneumonitis showed no difference in gender, immunosuppressive therapy,

days posttransplantation, comorbidity, or preexistent lung disease. Several points, however, are of interest. None of the de novo-treated patients except 4 patients (9.8%) with late administration of sirolimus developed interstitial pneumonitis. The 4 patients with interstitial pneumonitis tended to be older (58.7 ± 5.5 vs 46.9 ± 1.7 years) and received higher sirolimus doses (3.5 ± 0.5 vs 1.4 ± 0.2 mg/d) with greater trough levels (15.4 ± 2.9 vs 8.0 ± 1.2 μg/L) at the onset of symptoms. Most notably, all patients with interstitial pneumonitis had a loading dose at the start of therapy, and an increase in sirolimus dose (or trough level) within 3 weeks prior to the onset of symptoms. Additional potential risk factors identified from the literature include allograft dysfunction, hypervolemia, and male gender. With careful monitoring (or even exclusion from therapy) of patients at risk for the development of disease, we have had no case of sirolimus-associated interstitial pneumonitis since September 2004.

L27 ANSWER 2 OF 14 CAPLUS
2006:1070279 Document No. 145:410678 Methods for treating infectious disease exacerbated asthma using CpG oligonucleotides. Krieg, Arthur M.; De Sanctis, George Tilo; Underwood, Stephen Leslie; Jupp, Raymond Anthony; Schmidt, John A. (Coley Pharmaceutical Group, Inc., USA; Sanofi-Aventis U.S.P. LLC). U.S. Pat. Appl. Publ. US 2006229271 A1 20061012, 60pp. (English). CODEN: USXXCO. APPLICATION: US 2006-401093 20060410. PRIORITY: US 2005-669548P 20050408.
AB It has been discovered herein that CpG oligonucleotides (CpG ODN) are particularly effective in combating infections, and particularly upper respiratory tract virus, that are a cause of asthma exacerbations. In some aspects of the invention C-class CpG ODN are particularly effective for carrying out the methods. As shown in the Examples below, C-class CpG ODN induced a panel of IFN-associated genes in the mouse, including those for antiviral proteins, and protected against airway inflammation exacerbated by combined antigen and virus exposures.

L27 ANSWER 3 OF 14 SCISEARCH
2006:1051354 The Genuine Article (R) Number: 096WU. PEG-hirudin/iloprost coating of small diameter ePTFE grafts effectively prevents pseudointima and intimal hyperplasia development. Heise M (Reprint); Schmidmaier G; Husmann I; Heidenhain C; Schmidt J; Neuhaus P; Settmacher U. Univ Med, Charite, Dept Gen Surg, Augustenburger Pl 1, D-13353 Berlin, Germany (Reprint); Univ Med, Charite, Dept Gen Surg, D-13353 Berlin, Germany; Charite, Ctr Musculoskeletal Surg, D-13353 Berlin, Germany. michael.heise@charite.de. EUROPEAN JOURNAL OF VASCULAR AND ENDOVASCULAR SURGERY (OCT 2006) Vol. 32, No. 4, pp. 418-424. ISSN: 1078-5884. Publisher: W B SAUNDERS CO LTD, 32 JAMESTOWN RD, LONDON NW1 7BY, ENGLAND. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Objectives. Small diameter PTFE grafts are prone to thrombosis and intimal hyperplasia development. Heparin graft coating has beneficial effects but also potential drawbacks. The purpose of this study was to evaluate the experimental efficacy of PEG-hirudin/iloprost coated small caliber PTFE grafts.

Methods. Thirty-six femoro-popliteal ePTFE grafts (expanded polytetrafluoroethylene, diameter 4 mm) were inserted into 18 pigs. Grafts were randomised individually for each leg and grouped for 3 groups. Group 1 consisted of native ePTFE grafts, group II were grafts coated with a polylactide polymer (PLA) without drugs and group III grafts were coated with PLA containing a polyethylene glycol (PEG)-hirudin/iloprost combination. The follow-up period was 6 weeks. Patency rates were calculated and development of pseudointima inside the grafts was noted. Thickness of intimal hyperplasia at the distal anastomoses was

measured using light microscopy.

Results. Patency rates for group I were 6/9 (67%), for group II 9/10 (90%) and 12/12 (100%) for group III. In groups I and II there was a significant reduction of blood flow proximal to the graft at graft harvest, to 29 +/- 12 and 28 +/- 20 ml/min respectively (both p < 0.01 versus preoperative value), whilst in group III blood flow, 99 +/- 21 ml/min, remained at the preoperative level. Subtotal stenosis due to development of pseudointima was noted in each of the native and PLA coated grafts but not in group III grafts. Intimal hyperplasia at the distal anastomosis was lowest in group III.

Conclusions. The PEG-hirudin/iloprost coating of ePTFE prostheses effectively reduced pseudointima and intimal hyperplasia development and led to superior graft patency.

L27 ANSWER 4 OF 14 EMBASE

2006381737 EMBASE Phase II evaluation of docetaxel plus exisulind in patients with androgen independent prostate carcinoma. Sinibaldi V.J.; Elza-Brown K.; Schmidt J.; Eisenberger M.A.; Rosenbaum E.; Denmeade S.R.; Pili R.; Walczak J.; Baker S.D.; Zahurak M.; Carducci M.A.. Dr. V.J. Sinibaldi, Johns Hopkins Medical Institutions, 550 North Broadway, Baltimore, MD 21205, United States. sinibvi@jhmi.edu. American Journal of Clinical Oncology: Cancer Clinical Trials Vol. 29, No. 4, pp. 395-398 2006.

Refs: 12.

ISSN: 0277-3732. E-ISSN: 1537-453X. CODEN: AJCODI

00000421200608000000013. Pub. Country: United States. Language: English. Summary Language: English.

Entered STN: 20060823. Last Updated on STN: 20060823

AB OBJECTIVES: In this phase II study, the combination of docetaxel and exisulind (a GMP phosphodiesterase inhibitor) was given to patients with metastatic androgen independent prostate cancer (AIPC) to establish efficacy, assess toxicity, and determine pharmacokinetics of docetaxel administered alone and in combination with exisulind. METHODS: Fourteen patients with metastatic AIPC were registered to receive weekly docetaxel for 4 weeks, followed by 2 weeks of rest; repeated up to a maximum of 6 cycles. Exisulind 250 mg was given orally twice a day starting on day 8 of the study and taken continuously. RESULTS: All patients were evaluable for toxicity, response and survival. Grade 3 reversible toxicities included: fatigue, nausea, diarrhea, abdominal pain, rash, syncope, pulmonary edema, deep vein thrombosis, congestive heart failure, and elevations in transaminases, requiring therapy delays and/or dose reductions, or removal from therapy. Only 3 out of 14 patients (21.4%) had a 50% decline in prostate specific antigen (PSA) level that lasted ≥4 weeks; 1 out of 14 patients (7%) had a lymph node response. Median survival was 17.28 months. Docetaxel pharmacokinetics for 11 patients demonstrated mean ± SD clearance values that were similar during week 1 and week 3 when exisulind had been added. CONCLUSIONS: Overall, our trial indicated that the toxicity profile and efficacy of this regimen is unlikely to be substantially better than single agent docetaxel. Copyright .COPYRGT. 2006 by Lippincott Williams & Wilkins.

L27 ANSWER 5 OF 14 EMBASE

2006544211 EMBASE Immunosuppressive standards in simultaneous kidney-pancreas transplantation. Schmied B.M.; Muller S.A.; Mehrabi A.; Welsch Th.; Buchler M.W.; Zeier M.; Schmidt J.. Dr. B. Schmied, Chirurgische Klinik, Universitat Heidelberg, Im Neuenheimer Feld 110, D-69120 Heidelberg, Germany. bruno.schmied@med.uni-heidelberg.de. Clinical Transplantation Vol. 20, No. SUPPL. 17, pp. 44-50 2006.

Refs: 40.

ISSN: 0902-0063. E-ISSN: 1399-0012. CODEN: CLTRED
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20061122. Last Updated on STN: 20061122

AB Simultaneous pancreas-kidney transplantation is an established procedure for patients with type I diabetes and end-stage renal disease. Continuous advances in the operation techniques with consequent reduction of perioperative morbidity and mortality and the introduction of modern immunosuppressive agents improved not only patients but also graft survival and significantly decreased rejection episodes of both kidney and pancreas grafts. Availability of a variety of new immunosuppressants in the clinical routine and increasing experience of the transplant specialists allowed further developments of therapeutic schemes with application of induction and maintenance immunosuppressive protocols. In this article, we summarize the current status of immunosuppressive regimens in simultaneous pancreas and kidney transplantation.

L27 ANSWER 6 OF 14 EMBASE

2006544210 EMBASE The role and value of sirolimus administration in kidney and liver transplantation. Mehrabi A.; Fonouni H.; Kashfi A.; Schmied B.M.; Morath Ch.; Sadeghi M.; Schemmer P.; Encke J.; Sauer P.; Zeier M.; Weitz J.; Buchler M.W.; Schmidt J.. Dr. A. Mehrabi, Division of Visceral Transplantation, Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Heidelberg, Germany. arianeb_mehrabi@med.uni-heidelberg.de. Clinical Transplantation Vol. 20, No. SUPPL. 17, pp. 30-43 2006.
Refs: 58.
ISSN: 0902-0063. E-ISSN: 1399-0012. CODEN: CLTRED
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20061122. Last Updated on STN: 20061122

AB Enormous advancements in visceral transplantation have led to significant improvements in the quality of life of patients. However, despite these developments, the average graft half-life after transplantation has remained almost unchanged and chronic rejection is still considered a major problem. In this regard, more concerns have shifted to factors influencing long-term graft survival, patient survival, and quality of life. To achieve this goal, detrimental effects of immunosuppressive (IS) agents, which have deleterious influence on the quality of life and/or patient survival, should be reduced. In the course of recent years, the transplant community has worked on reducing these side effects by developing new ISs, employing new combination regimens, or finding and adjusting optimal dosages and blood level concentrations. Among the IS agents, the antifungal, antitumoral and IS activity of mammalian target of rapamycin (mTOR) inhibitors without nephrotoxicity, have received special attention regarding this new class of IS. Sirolimus (SRL), as the first member of mTOR inhibitors, has been utilized in many clinical trials with respect to its benefit-risk assessment. In our review, the clinical evolution of SRL, as well as the evidence-based clinical benefits of SRL in kidney and liver transplantation (KTx, LTx), are summarized. Various studies of SRL in KTx and LTx have shown that combination therapy with SRL will enrich the variety of IS modalities. It also can be regarded as a safe base therapy to which other necessary drugs can be added. In addition to the enhanced acute rejection prophylaxis, and in contrast to the calcineurin inhibitors (CNI) and steroids, this drug solely does not have common side effects such as nephrotoxicity, neurotoxicity, diabetes mellitus and hypertension. Moreover, this agent might diminish vasculopathic processes that mediate chronic allograft nephropathy (CAN). Therefore, by reducing the likelihood of CAN it can decrease the rate of long-term organ failure.

One possibly desirable characteristic of SRL is its antiproliferative effect, which could provoke antitumoral or antiatherogenic activity following transplantation. Despite all promising impacts of SRL in organ transplantation, there are some concerns regarding the adverse effects of this drug, for instance dyslipidemia, pneumonitis and wound healing problems. However, the majority of these side effects can be reduced or ceased by careful dose adjustments and correct timing of use. In conclusion, after a decade of both in vivo and in vitro studies on SRL, it can be advocated that SRL is a promising, potent and effective IS agent as it reduces the rate of acute rejection episodes in de novo transplants. It could improve the quality of life, graft and patient survival rate, and achieve excellent outcomes with few adverse effects when wisely used in combination with other immunosuppressants. .COPYRGT. 2006 Blackwell Munksgaard.

L27 ANSWER 7 OF 14 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2005:479942 Document No.: PREV200510266527. Cytotoxic activity of cytokine-induced killer cells correlates with expression of SAP and SLAM. Mehrle, Stefan [Reprint Author]; Frank, Susanne; Schmidt, Jan; Buchler, Markus W.; Schmidt-Wolf, Ingo G. H.; Marten, Angela. Univ Heidelberg, Dept Surg, D-6900 Heidelberg, Germany. Blood, (NOV 16 2004) Vol. 104, No. 11, Part 2, pp. 55B-56B.
Meeting Info.: 46th Annual Meeting of the American-Society-of-Hematology. San Diego, CA, USA. December 04 -07, 2004. Amer Soc Hematol.
CODEN: BLOOAW. ISSN: 0006-4971. Language: English.
AB SAP is a small protein, consisting of a single SH2 domain which is mutant in humans with X-linked lymphoproliferative disease. Patients with XLP are affected by fatal EBV infections and malignant B cell lymphomas. The increased risk for B cell lymphomas is suggested to result from impaired immunosurveillance ofB cell proliferation by T cells. Here, we investigated the role of SLAM/SAP for activation of effector cells with cytotoxic activity (CIK cells), which aregenerated by unspecific stimulation of the T cell receptor and addition of exogenous IL-2 as described previously. The TCR activation on day +1 resulted not only in a short, peak of activated cells, but activation continued and increased in combination with IL-2. We observed a striking peak of SLAM (Signaling Lymphocyte Activation Molecule) on day +6 in form of extracellular detectable CD150 as well as at the level of proteins and mRNA. Interestingly, the cytotoxic activity and the amount of SHP-2 protein showed a similar pattern as the parameters mentioned above but were shifted one day. Comparing these data for correlation, we observed a significant correlation between cytotoxic activity and CD150 expression pattern ($P<0.001$) and amount of SLAM protein ($P<0.02$) as well as between amount of SHP-2 protein and SLAM parameters ($P<0.03$). IL-10 secretion did not correlate with any of the parameters investigated. Secretion of Th1/Th2 cytokines was determined using a cytometric bead assay. There was no change in the amount of IL-6 and TNF-alpha. IL-4 was below the detection threshold and IL-2 could not be analyzed due to exogenous addition. IFN-gamma levelsincreased during cultivation, peaked on day +3 and then remained at about 4ng/ml. IL-10 secretion started after stimulation of cells by anti-CD3, peaked onday +3 and then decreased continuously. Between day +6 and day +7. only 0.86 +/- 0.02ng/ml/24hrs/3x 10(6) cells were secreted. In summary, activation of peripheral blood cells with agonistic anti-CD3 antibody and exogenous IL-2. as used for generation of CIK cells, results in significant SLAM and SAP activation five days after TCR stimulation. This peak correlates with cytotoxic activity against tumor cells. SLAM expression and binding by SAP seems to beimportant in the activation of cytotoxic effector cells.

L27 ANSWER 8 OF 14 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
2004366326 EMBASE Long-term results of paediatric kidney transplantation at

the University of Heidelberg: A 35 year single-centre experience. Mehrabi A.; Kashfi A.; Tonshoff B.; Feneberg R.; Mehls O.; Schemmer P.; Kraus T.; Wiesel M.; Buchler M.W.; Schmidt J.. Dr. J. Schmidt, Dept. of Gen. Visc./Transplant Surg., University of Heidelberg, IFN 110, 69120 Heidelberg, Germany. jan_schmidt@med.uni-heidelberg.de. Nephrology Dialysis Transplantation Vol. 19, No. SUPPL. 4, pp. iv69-iv74 2004. Refs: 23.
ISSN: 0931-0509. CODEN: NDTREA
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20040916. Last Updated on STN: 20040916

AB Background. Kidney transplantation remains the most effective treatment for children with end-stage renal disease. We analysed data from the University of Heidelberg transplant programme to present our results on paediatric kidney transplantations over the past 35 years. Methods. From 1967 to 2003, 354 paediatric kidney transplantations were performed at the University of Heidelberg. Data were obtained from the paediatric kidney transplantation records consisting of 291 (82%) cadaveric and 63 (18%) living donated transplants. Demographic data, family relationship of the living donors, surgical technique, immunosuppressive drugs, graft and patient survival rates were assessed. Results. The mean age of cadaveric and living donors was 32.0 ± 17.1 and 37.6 ± 7.5 years, respectively. The family relationship of the living donors included the mother in 65% of cases, the father in 31%, and other relatives in 4%. In the last 4 years, the respective mean cold ischaemia time was 1.6 ± 0.5 h for living donated and 13.5 ± 4.1 h for cadaveric donors. The mean age of children who received kidneys from cadaveric and living donors was 11.3 ± 4.5 and 10.4 ± 4.5 years, respectively, with a male to female ratio of 57 to 43%. Overall patient survival rates were 95% after 1 year and 89% after 5 years. The patient 5 and 10 year survival rates for living donor renal transplantations were 95 and 95%, respectively. Graft survival rates improved since 1990 compared with the period prior to 1990: 82.5 vs 56.7% graft survival at 1 year and 82.5 vs 50% after 5 years (P = 0.03). Comparing the operating technique in a subgroup of our patients that received the same immunosuppressive regimen, anastomoses with the aorta and vena cava (51%, n = 31) were associated with a graft survival of 86.6 and 83.3% after 1 and 5 years, whereas anastomoses with iliac vessels (49%, n = 30) were associated with a graft survival of 55.8 and 51.6% after 1 and 5 years, respectively (P = 0.01). Conclusions. There has been a gradual improvement in our paediatric kidney transplantation results over time. Living donor paediatric kidney transplants have higher patient and better graft survival rates than cadaveric donor kidney transplants. Using the aorta and inferior vena cava for graft anastomosis, utilizing newer immunosuppressive drugs and implementing living kidney donation have positively affected the results of our paediatric kidney transplantations.

L27 ANSWER 9 OF 14 MEDLINE on STN DUPLICATE 1

2003358443. PubMed ID: 12891121. Inducible nitric oxide synthase is present in human abdominal aortic aneurysm and promotes oxidative vascular injury. Zhang Jian; Schmidt Jan; Ryschich Eduard; Mueller-Schilling Martina; Schumacher Hardy; Allenberg Jens Rainer. (Third General Surgery Department, First Affiliated Hospital, China Medical University, Shenyang 110001, China.. jianzhang_cmu@yahoo.com.cn) . Journal of vascular surgery : official publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter, (2003 Aug) Vol. 38, No. 2, pp. 360-7. Journal code: 8407742. ISSN: 0741-5214. Pub. country: United States. Language: English.

AB OBJECTIVE: Nitric oxide (NO), catalyzed by inducible NO synthase (iNOS), may be important in the pathophysiologic characteristics of many vascular diseases. Although there is indirect evidence to support the presence of

iNOS in abdominal aortic aneurysm (AAA) in human beings, no definitive study has confirm this finding. The present study was designed to assess expression of iNOS in AAA in human beings. Furthermore, the activity of iNOS and the oxidative vascular injury initiated by iNOS were assessed with detection of nitrotyrosine, which is a marker indicative of formation and activity of the NO-derived oxidant peroxynitrite. METHODS: We studied 25 patients with AAA and 10 patients with normal abdominal aortas. In situ hybridization and immunohistochemistry were used in tissue sections to localize iNOS messenger RNA (mRNA) and protein. Double staining with a combination of in situ hybridization and immunohistochemistry was used to simultaneously demonstrate iNOS mRNA expression and its cellular localization. The presence of peroxynitrite was indirectly assessed with immunostaining with anti-nitrotyrosine antibodies. RESULTS: In situ hybridization and immunohistochemistry confirmed the presence of iNOS in media and adventitia of AAA in all 25 patients. Specific cell markers identified iNOS mRNA-positive cells mainly as T and B lymphocytes, macrophages, and smooth muscle cells. Positive immunostaining for nitrotyrosine was present in macrophages and smooth muscle cells. Normal abdominal aorta demonstrated virtually no iNOS or nitrotyrosine expression. CONCLUSION: Stimulated expression of iNOS is associated with degeneration of AAA in human beings, and the activity of this enzyme under such conditions preferentially promotes formation and activity of peroxynitrite and further contributes to oxidative tissue and cellular injury in AAA. This may be important in the pathogenesis of AAA.

L27 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN

2002:539555 Document No. 137:108304 Pharmaceutical compositions comprising Receptor tyrosine kinase-inhibiting antibodies and angiogenesis inhibitors for treating cancer and metastasis. Goodman, Simon; Kreysch, Hans-Georg (Merck Patent Gmbh, Germany). PCT Int. Appl. WO 2002055106 A2 20020718, 45 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-EP15241 20011221. PRIORITY: EP 2001-100507 20010109.

AB The invention relates to a combination therapy for the treatment of tumors and tumor metastases comprising administration of receptor tyrosine kinase antagonists/inhibitors, especially ErbB receptor antagonists, more preferably EGF receptor (Her 1) antagonists and anti-angiogenic agents, preferably integrin antagonists, optionally together with agents or therapy forms that have additive or synergistic efficacy when administered together with said combination of antagonists/inhibitors, such as chemotherapeutic agents and or radiation therapy. The therapy can result in a synergistic potential increase of the inhibition effect of each individual therapeutic on tumor cell proliferation, yielding more effective treatment than found by administering an individual component alone.

L27 ANSWER 11 OF 14 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

1998217602 EMBASE Hepatitis C virus dynamics in vivo: Effect of ribavirin and interferon alfa on viral turnover. Zeuzem S.; Schmidt J.M.; Lee J.-H.; Von Wagner M.; Teuber G.; Roth W.K.. Dr. S. Zeuzem, Medizinische Klinik II, Zentrum der Inneren Medizin, Klin. Johann Wolfgang Goethe-Univ., Theodor-Stern-Kai 7, D-60590 Frankfurt a.M., Germany. Hepatology Vol. 28, No. 1, pp. 245-252 1998.
Refs: 36.

ISSN: 0270-9139. CODEN: HPTLD
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 19980904. Last Updated on STN: 19980904

AB Treatment of patients with chronic hepatitis C with recombinant interferon alfa (rIFN-α) can cause a decrease of serum transaminases and hepatitis C virus (HCV) RNA. Recent trials evaluating combination therapy of IFN-α and ribavirin suggested a potential synergistic effect. From serial measurements of serum HCV RNA concentrations following treatment-induced perturbation of the balance between virus production and clearance, we compared the antiviral efficacy of both IFN-α alone and IFN-α in combination with ribavirin. Chronically HCV-infected patients were treated with either 3 x 3 MU or 3 x 6 MU rIFN-α per week or 3 x 6 MU rIFN-α plus 14 mg/kg of body weight ribavirin per day The time-dependent HCV RNA concentrations during antiviral treatment were analyzed by iterative least- squares regression. After initiation of antiviral therapy, HCV RNA declined exponentially below the detection limit of the reverse-transcription polymerase chain reaction assay (1,000 HCV RNA molecules per milliliter) in 10 of 26 (39%), 10 of 19 (53%), and 10 of 18 patients (56%) treated with 3 x 3 MU, 3 x 6 MU rIFN-α without and with ribavirin, respectively Viral clearance from serum was faster in patients treated with 3 x 6 MU rIFN-α ($t(1/2) = 0.23 \pm 0.15$) compared with patients treated with 3 x 3 MU rIFN-α per week (0.67 ± 0.36 days) ($P < .004$). However, half-lives of viral clearance were similar in patients treated with rIFN-α or rIFN-α plus ribavirin. For virus release from infected hepatocytes, absence and presence of ribavirin yielded half-lives of $t(1/2) = 2.54 \pm 2.10$ and $t(1/2) = 1.99 \pm 1.70$, respectively, indicating that ribavirin does not significantly inhibit HCV production. In conclusion, the data of the present study indicate that higher rIFN-α doses accelerate viral clearance from serum. Ribavirin (14 mg/kg/d), however, lacks synergistic antiviral effects in the treatment of chronic hepatitis C with 3 x 6 MU rIFN-α per week.

L27 ANSWER 12 OF 14 MEDLINE on STN

94350639. PubMed ID: 8071057. Effect of corticosteroids, cyclosporin A, and methotrexate on cytokine release from monocytes and T-cell subsets. Schmidt J; Fleissner S; Heimann-Weitschat I; Lindstaedt R; Pomberg B; Werner U; Szelenyi I. (Department of Pharmacology, ASTA Medica AG, Frankfurt/Main, Germany.) Immunopharmacology, (1994 May-Jun) Vol. 27, No. 3, pp. 173-9. Journal code: 7902474. ISSN: 0162-3109. Pub. country: Netherlands. Language: English.

AB Corticosteroids are the most effective drugs in the management of asthma. However, because of their known side effects and the existence of corticosteroid-resistant patients, there is a need for substitute medications in asthma therapy. Using cell lines, in the present study, the two corticosteroids dexamethasone (Dex), and beclomethasone (Bec), as well as the immunosuppressant cyclosporin A (CsA), and the antimetabolic drug methotrexate (Mtx) were examined in their effect on release of immunoreactive IL-1 beta, IL-2, IL-4, IL-5, and IL-8. THP-1 cells served as a test model for monocytes secreting IL-1 beta and IL-8 upon stimulation by lipopolysaccharide. Jurkat cells were used as a test model for TH1-type T-cells and were stimulated for IL-2 release with a combination of phytohemagglutinin and phorbol myristate acetate. Representing TH2-type T-cells, D10.G4.1 cells challenged by anti-CD3-mAb produced IL-4, and IL-5. Considerable qualitative and quantitative differences in the relative efficacy of the test compounds were found. Following IC50 values (nmol/l) of the test compounds were estimated (IL-1 beta/IL-8/IL-2/IL-4/IL-5): Dex (10.8/35.7/ > 10,000.0/5.1/4.1), Bec (30.9/102.2/8591.4/0.6/0.4), and CsA (318.7/6211.2/2.3/68.2/237.9). Mtx in concentrations up to 10,000.0 nmol/l was completely inactive. It can be concluded that corticosteroids show another inhibition pattern than CsA: corticosteroids affect mainly TH2-type T-cells, while CsA primarily

inhibits the TH1-type T-cell response.

L27 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
1982:102117 Document No. 96:102117 Monoclonal antibodies to the human leukocyte interferons and their use for interferon purification and a quantitative interferon assay. Staehelin, Theophil; Takacs, Bela; Durrer, Brigitte; Schmidt, Joerg; Stocker, John; Miggiano, Vincenzo; Staehli, Christian; Hobbs, Donna S.; Kung, Hsiang Fu; Pestka, Sidney (Pharma Res. Div., F. Hoffmann-La Roche and Co. Ltd., Basel, CH-4002, Switz.). Symposia of the Giovanni Lorenzini Foundation, 11(Monoclonal Antibodies Dev. Immunoassay), 79-85 (English) 1981. CODEN: SGLFD9. ISSN: 0166-1167.
AB A collection of 12 monoclonal antibodies to human leukocyte interferon is discussed. The antibodies comprise 4 different heavy- light-chain isotype combinations. Antibody -binding and interferon-neutralization results suggest that at least 3 distinct epitopes of human leukocyte interferons can be recognized and defined by these monoclonal antibodies.

L27 ANSWER 14 OF 14 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
80223022 EMBASE Document No.: 1980223022. Biochemical methods in the treatment of sexual disorders. Schmidt Jr. C.W.. Dept. Psychiat., Baltimore City Hosp., Baltimore, Md. 21224, United States. Psychiatric Clinics of North America Vol. 3, No. 1, pp. 189-199 1980. CODEN: PCAMDG
Pub. Country: United States. Language: English.
Entered STN: 911209. Last Updated on STN: 911209
AB Future biochemical treatment of sexual disorders will follow developments in brain neurochemistry and will bring about combinations of psychopharmacologic methods. However, the success in creating multimodal treatments will require interdisciplinary collaboration.

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                   searching
 NEWS  7  MAY 30   DGENE, PCTGEN, and USGENE enhanced with new homology
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 NEWS  9  JUN 06   KOREAPAT updated with 41,000 documents
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                   patent numbers for U.S. applications
 NEWS 11  JUN 19   CAS REGISTRY includes selected substances from
                   web-based collections
 NEWS 12  JUN 25   CA/CAplus and USPAT databases updated with IPC
                   reclassification data
 NEWS 13  JUN 30   AEROSPACE enhanced with more than 1 million U.S.
                   patent records
 NEWS 14  JUN 30   EMBASE, EMBAL, and LEMBASE updated with additional
                   options to display authors and affiliated
                   organizations
 NEWS 15  JUN 30   STN on the Web enhanced with new STN AnaVist
                   Assistant and BLAST plug-in
 NEWS 16  JUN 30   STN AnaVist enhanced with database content from EPFULL
 NEWS 17  JUL 28   CA/CAplus patent coverage enhanced
 NEWS 18  JUL 28   EPFULL enhanced with additional legal status
                   information from the epoline Register
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 NEWS 20  JUL 28   STN Viewer performance improved
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 NEWS 22  AUG 13   CA/CAplus enhanced with printed Chemical Abstracts
                   page images from 1967-1998
 NEWS 23  AUG 15   CAOLD to be discontinued on December 31, 2008
 NEWS 24  AUG 15   CAplus currency for Korean patents enhanced
 NEWS 25  AUG 25   CA/CAplus, CASREACT, and IFI and USPAT databases
                   enhanced for more flexible patent number searching
 NEWS 26  AUG 27   CAS definition of basic patents expanded to ensure
                   comprehensive access to substance and sequence
                   information

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FILE 'CAPLUS' ENTERED AT 17:06:20 ON 27 AUG 2008

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L1   3657154 COMPOSITION

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L2   72284 L1 AND ANTIBOD?

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L9   0 L7 AND H425

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L11  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2008 ACS on STN
1989:129272   Document No. 110:129272  Original Reference No. 110:21199a,21202a
     A soluble brain molecule related to epidermal growth factor receptor is a
     mitogen inhibitor for astrocytes.  Nieto-Sampedro, Manuel; Broderick, J.
     T. (Dep. Psychobiol., Univ. California, Irvine, CA, 92717, USA).  Journal
     of Neuroscience Research, 22(1), 28-35 (English) 1989.  CODEN:
     JNREDK.  ISSN: 0360-4012.
AB   The astrocyte mitogenic activity of normal and injured rat brain exts. was
     greatly enhanced by antibodies to EGF receptor (EGFR).  The
     antibodies appear to act by removing from the exts. inhibitory
     mols. immunol. related to EGFR.  Three mol. species recognized by
     anti-EGFR antibody in brain exts. (mol. wts.
     41, 52, and 69 kilodaltons) did not seem to originate from EGFR
     proteolysis.  The increase in astrocyte mitogenic activity in brain tissue
     following injury correlated with a reduction in the levels of soluble
     EGFR-cross-reacting material and a decrease in mitogen inhibitory
     activity.  The decrease in EGFR-related mitogen inhibitor also correlated
     with a large increase in astrocyte membrane EGFR immunoreactivity, and
     intracerebral injection of antibodies to EGFR caused the
     appearance at the injection site of numerous EGFR-pos. reactive
     astrocytes.  Invasion of brain tissue by EGF/EGFR-related blood components
     may be the signal that initiates astrocyte activation.  EGFR-related
     immunoreactive mols. are also present in exts. of other tissues and may
     have a general role in the control of cell division.

L11  ANSWER 2 OF 2  CAPLUS  COPYRIGHT 2008 ACS on STN
1986:528337   Document No. 105:128337  Original Reference No. 105:20601a,20604a
     Changes in epidermal growth factor receptor distribution and function
     during epidermal maturation.  Green, Martin R.; Smith, Colin G. (Biosci.
     Div., Unilever Res., Sharnbrook/Bedford, MK44 1LQ, UK).  Biochemical
     Society Transactions, 14(6), 1032-3 (English) 1986.  CODEN:
     BCSTB5.  ISSN: 0300-5127.
AB   EGF  [62229-50-9] receptor (EGFR) distribution and ultrastructural
     localization were determined by immunohistochem. methods with 3 different
     antibodies (EGF-R1, 2E9, and anti-EGFR) in
     fresh, human scalp skin and foreskin.  Antibody patterns were
     similar though antibodies 2E9 and anti-EGFR
     did not recognize the lower basal epidermal cell membrane on the papillary
     epidermis.  Antibody EGF-R1 gave partial recognition in this
     area.  EGFR were found near the plasma membrane, intracellularly, and over
     the cell nucleus in epidermal basal cells.  125I-labeled EGF (125I-EGF)
     was internalized and after 2.5 h the distribution of 125I-EGF was qual.
     similar to that shown for the receptor.  EGFR were also observed in the upper
     epidermis with a proportion of the receptors located proximal to the
     cytoplasmic face of the membrane.  These cells failed to bind 125I-EGF
     which suggests inaccessability of the receptors.  Changes in membrane
     composition during maturation could account for these differences in
     binding patterns.


=> s l2 and cetuximab
L12          88 L2 AND CETUXIMAB

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L13 3 L12 AND EMD72000

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L14 3 DUP REMOVE L13 (0 DUPLICATES REMOVED)

=> d l14 1-3 cbib abs

L14 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2008 ACS on STN
2008:380887 Document No. 148:394375 Method for treating cancer harboring EGFR mutations. Solca, Flavio (Boehringer Ingelheim International G.m.b.H., Germany; Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G.). PCT Int. Appl. WO 2008034776 A1 20080327, 60pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, MT, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2007-EP59735 20070914. PRIORITY: EP 2006-120856 20060918; EP 2007-101505 20070131.

AB The present invention relates to a method of treatment of patients suffering from cancer and harboring mutations of EGFR in the tumor, for instance an activating mutation of the EGFR or a mutation responsible for resistance or the emergence of acquired resistance to treatment with reversible EGFR and/or HER2 inhibitors or irreversible inhibitors such as CI-1033, EKB-569, HKI-272 or HKI-357, comprising administering an effective amount of the irreversible EGFR inhibitor BIBW2992 (4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline), to a person in need of such treatment, optionally in combination with the administration of a further chemotherapeutic agent, in combination with radiotherapy, radio-immunotherapy and/or tumor resection by surgery, and to the use of a BIBW2992 for preparing a pharmaceutical composition for the treatment of patients suffering from cancer and harboring mutations of EGFR in the tumor.

L14 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2008 ACS on STN
2007:83399 Document No. 146:177214 Use of EGFR inhibitors to prevent or treat obesity. Threadgill, David; Barrick, Cordelia Johnson (The University of North Carolina At Chapel Hill, USA). PCT Int. Appl. WO 2007011702 A2 20070125, 74pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2006-US27316 20060714. PRIORITY: US 2005-699671P 20050715.

AB Methods of treating or preventing obesity or obesity related disorders in a subject are provided, comprising administering to the subject a treatment effective in reducing one or more activities of an epidermal growth factor receptor (EGFR) in the subject. Methods of screening for compns. that can modulate one or more EGFR activities are also provided.

L14 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2008 ACS on STN
2007:63312 Document No. 146:115067 EGFR inhibitors promote axon

regeneration. He, Zhigang; Koprivica, Vuk (Children's Medical Center Corporation, USA). PCT Int. Appl. WO 2007008338 A1 20070118, 23pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2006-US23431 20060613. PRIORITY: US 2005-180070 20050712.

AB The invention discloses compns. and methods for promoting neural regeneration in a patient determined to have a lesion in a mature CNS neuron. The method comprises contacting the neuron with an EGFR inhibitor sufficient to promote regeneration of the neuron.

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=> s cetuximab
L15       8561 CETUXIMAB

=> s l15 and EMD72000
L16         41 L15 AND EMD72000

=> s l16 and pd<20021010
   1 FILES SEARCHED...
   4 FILES SEARCHED...
L17          0 L16 AND PD<20021010

=> s l15 and humanized
L18        238 L15 AND HUMANIZED

=> s l18 and "h425"
L19          0 L18 AND "H425"

=> dup remove l16
PROCESSING COMPLETED FOR L16
L20          22 DUP REMOVE L16 (19 DUPLICATES REMOVED)

=> d l20 1-22 cbib abs

L20  ANSWER 1 OF 22  CAPLUS  COPYRIGHT 2008 ACS on STN
2008:806157   Document No. 149:126547  Treatment of diabetes by at least one
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epidermal growth factor receptor specific antibody or a derivative thereof. Selzer, Edgar; Kornek, Gabriela (Novelix Therapeutics G.m.b.H., Austria). PCT Int. Appl. WO 2008077171 A1 20080703, 18pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, MT, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2007-AT584 20071221. PRIORITY: AT 2006-2135 20061222.

AB The present invention relates to the use of at least one epidermal growth factor receptor (EGFR) specific antibody or a derivative thereof for the manufacture of a medicament for the treatment of diabetes, in particular of the advanced insulin-dependent stage of diabetes mellitus type 1 and 2 in humans as well as in animals. An example describes that the administration of Cetuximab (Erbitux), an EGFR type I-specific antibody to a patient with a 21-yr. history of insulin-dependent type 2

diabetes, led to a loss of insulin dependency after combined treatment with Cetuximab and radiotherapy for locally advanced oropharyngeal cancer.

L20 ANSWER 2 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN
2008:380887 Document No. 148:394375 Method for treating cancer harboring EGFR mutations. Solca, Flavio (Boehringer Ingelheim International G.m.b.H., Germany; Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G.). PCT Int. Appl. WO 2008034776 A1 20080327, 60pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, MT, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2007-EP59735 20070914. PRIORITY: EP 2006-120856 20060918; EP 2007-101505 20070131.

AB The present invention relates to a method of treatment of patients suffering from cancer and harboring mutations of EGFR in the tumor, for instance an activating mutation of the EGFR or a mutation responsible for resistance or the emergence of acquired resistance to treatment with reversible EGFR and/or HER2 inhibitors or irreversible inhibitors such as CI-1033, EKB-569, HKI-272 or HKI-357, comprising administering an effective amount of the irreversible EGFR inhibitor BIBW2992 (4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline), to a person in need of such treatment, optionally in combination with the administration of a further chemotherapeutic agent, in combination with radiotherapy, radio-immunotherapy and/or tumor resection by surgery, and to the use of a BIBW2992 for preparing a pharmaceutical composition for the treatment of patients suffering from cancer and harboring mutations of EGFR in the tumor.

L20 ANSWER 3 OF 22 MEDLINE on STN DUPLICATE 1
2008083659. PubMed ID: 18033688. Matuzumab and cetuximab activate the epidermal growth factor receptor but fail to trigger downstream signaling by Akt or Erk. Yoshida Takeshi; Okamoto Isamu; Okabe Takafumi; Iwasa Tsutomu; Satoh Taroh; Nishio Kazuto; Fukuoka Masahiro; Nakagawa Kazuhiko. (Department of Medical Oncology, Kinki University School of Medicine, Osaka, Japan.) International journal of cancer. Journal international du cancer, (2008 Apr 1) Vol. 122, No. 7, pp. 1530-8. Journal code: 0042124. E-ISSN: 1097-0215. Pub. country: United States. Language: English.

AB Molecular inhibition of the epidermal growth factor receptor (EGFR) is a promising anticancer strategy, and monoclonal antibodies (mAbs) to EGFR are undergoing extensive evaluation in preclinical and clinical trials. However, the effects of anti-EGFR mAbs on EGFR signaling have remained unclear. We have now examined the effects of 2 anti-EGFR mAbs, matuzumab (EMD72000) and cetuximab (Erbitux), both of which are currently under assessment for treatment of various cancers, on EGFR signal transduction and cell survival in nonsmall cell lung cancer cell lines. Similar to EGF, matuzumab and cetuximab each induced phosphorylation of EGFR at several tyrosine phosphorylation sites as a result of receptor dimerization and activation of the receptor tyrosine kinase. In contrast to the effects of EGF, however, EGFR activation induced by these antibodies was not accompanied by receptor turnover or by activation of downstream signaling pathways that are mediated by Akt and Erk and are important for regulation of cell proliferation and survival. In addition, clonogenic survival assays revealed that matuzumab and cetuximab reduced the survival rate of H292 cells, in which they

also inhibited the EGF-induced activation of Akt and Erk. Although we have examined only a few cell lines, our results indicate that the antitumor effects of matuzumab and cetuximab depend on inhibition of EGFR downstream signaling mediated by Akt or Erk rather than on inhibition of EGFR itself.

L20 ANSWER 4 OF 22 MEDLINE on STN DUPLICATE 2
2008235941. PubMed ID: 18394559. Matuzumab binding to EGFR prevents the conformational rearrangement required for dimerization. Schmiedel Judith; Blaukat Andree; Li Shiqing; Knochel Thorsten; Ferguson Kathryn M. (Department of Physiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA.) Cancer cell, (2008 Apr) Vol. 13, No. 4, pp. 365-73. Journal code: 101130617. ISSN: 1535-6108. Pub. country: United States. Language: English.
AB An increasing number of therapeutic antibodies targeting tumors that express the epidermal growth factor receptor (EGFR) are in clinical use or late stages of clinical development. Here we investigate the molecular basis for inhibition of EGFR activation by the therapeutic antibody matuzumab (EMD72000). We describe the X-ray crystal structure of the Fab fragment of matuzumab (Fab72000) in complex with isolated domain III from the extracellular region of EGFR. Fab72000 interacts with an epitope on EGFR that is distinct from the ligand-binding region on domain III and from the cetuximab/Erbitux epitope. Matuzumab blocks ligand-induced receptor activation indirectly by sterically preventing the domain rearrangement and local conformational changes that must occur for high-affinity ligand binding and receptor dimerization.

L20 ANSWER 5 OF 22 CAPLUS
2007:83399 Document No. 146:177214 Use of EGFR inhibitors to prevent or treat obesity. Threadgill, David; Barrick, Cordelia Johnson (The University of North Carolina At Chapel Hill, USA). PCT Int. Appl. WO 2007011702 A2 20070125, 74pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2006-US27316 20060714. PRIORITY: US 2005-699671P 20050715.
AB Methods of treating or preventing obesity or obesity related disorders in a subject are provided, comprising administering to the subject a treatment effective in reducing one or more activities of an epidermal growth factor receptor (EGFR) in the subject. Methods of screening for compns. that can modulate one or more EGFR activities are also provided.

L20 ANSWER 6 OF 22 CAPLUS
2007:63312 Document No. 146:115067 EGFR inhibitors promote axon regeneration. He, Zhigang; Koprivica, Vuk (Children's Medical Center Corporation, USA). PCT Int. Appl. WO 2007008338 A1 20070118, 23pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2006-US23431 20060613. PRIORITY: US 2005-180070 20050712.

AB The invention discloses compns. and methods for promoting neural regeneration in a patient determined to have a lesion in a mature CNS neuron. The method comprises contacting the neuron with an EGFR inhibitor sufficient to promote regeneration of the neuron.

L20 ANSWER 7 OF 22 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

2007326811 EMBASE Rational bases for the development of EGFR inhibitors for cancer treatment.

Bianco, Roberto (correspondence); Gelardi, Teresa; Damiano, Vincenzo; Tortora, Giampaolo. Dipartimento di Endocrinologia e Oncologia Molecolare e Clinica, Universita di Napoli Federico II, Via S. Pansini 5, 80131 Napoli, Italy. robianco@unina.it. Ciardiello, Fortunato. Dipartimento Medico-Chirurgico, Internistica Clinica e Sperimentale, Seconda Universita di Napoli, Napoli, Italy.

International Journal of Biochemistry and Cell Biology Vol. 39, No. 7-8, pp. 1416-1431 2007.

Refs: 193.

ISSN: 1357-2725. CODEN: IJBBFU

S 1357-2725(07)00149-5. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Growth factor receptors and their ligands not only regulate normal cell processes but have been also identified as key regulators of human cancer formation. The epidermal growth factor receptor (EGFR/ErbB1/HER1) belongs to the ErbB/HER-family of tyrosine kinase receptors (RTKs). These trans-membrane proteins are activated following binding with peptide growth factors of the EGF-family of proteins. Several evidences suggest that cooperation of multiple ErbB receptors and ligands is required for the induction of cell transformation. In this respect, EGFR, upon activation, sustains a complex and redundant network of signal transduction pathways with the contribution of other trans-membrane receptors. EGFR has been found to be expressed and altered in a variety of malignancies and clearly it plays a significant role in tumor development and progression, including cell proliferation, regulation of apoptotic cell death, angiogenesis and metastatic spread. Moreover, amplification of the EGFR gene and mutations in the EGFR tyrosine kinase domain have been recently reported in human carcinomas. As a result, investigators have developed approaches to inhibit the effects of EGFR activation, with the aim of blocking tumor growth and invasion. A number of agents targeting EGFR, including specific antibodies directed against its ligand-binding domain and small molecules inhibiting its tyrosine kinase activity are either in clinical trials or are already approved for clinical treatment. This article reviews the EGFR role in carcinogenesis and tumor progression as rational bases for the development of specific therapeutic inhibitors. .COPYRGT. 2007 Elsevier Ltd. All rights reserved.

L20 ANSWER 8 OF 22 MEDLINE on STN

2007106668. PubMed ID: 17126894. A phase II trial of EMD72000 (matuzumab), a humanized anti-EGFR monoclonal antibody, in patients with platinum-resistant ovarian and primary peritoneal malignancies. Seiden M V; Burris H A; Matulonis U; Hall J B; Armstrong D K; Speyer J; Weber J D A; Muggia F. (Massachusetts General Hospital, 100 Blossom Street, Cox 640, Boston, MA 02114, USA.. mseiden@partners.org) . Gynecologic oncology, (2007 Mar) Vol. 104, No. 3, pp. 727-31. Electronic Publication: 2006-11-28. Journal code: 0365304. ISSN: 0090-8258. Pub. country: United States. Language: English.

AB OBJECTIVE: The primary objective of this study was to determine the rate of response to matuzumab in patients with recurrent, EGFR-positive ovarian, or primary peritoneal cancer. Secondary end points included safety and tolerability, time to tumor progression, duration of response, and overall survival. METHODS: A multi-institutional single arm phase II trial. RESULTS: Of 75 women screened for the study, 37 were enrolled and

treated. Median age of the treated patient population was 58 years, and most patients had more than four prior lines of chemotherapy. Therapy was well tolerated, the most common toxicities being a constellation of skin toxicities, including rash, acne, dry skin, and paronychia, as well as headache, fatigue, and diarrhea. Serious adverse events were very rare but included a single episode of pancreatitis that may have been drug related. All patients completed therapy, receiving 1 to 30 infusions of matuzumab. There were no formal responses (RR=0%, 95% CI: 0-9.5%), although 7 patients (21%) were on therapy for more than 3 months with stable disease. CONCLUSIONS: Matuzumab at the dose and schedule selected is well tolerated. In this population of very heavily pretreated patients with epithelial ovarian and primary peritoneal malignancies, there was no evidence of significant clinical activity when matuzumab was administered as monotherapy.

L20 ANSWER 9 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN
2007:434047 Document No. 147:22175 Current status of monoclonal antibody for metastatic colorectal cancer. Kojima, Takashi; Doi, Toshihiko; Ohtsu, Atsushi (Div. GI Oncol./Digestive Endoscopy, National Cancer Center Hospital East, Japan). Saishin Igaku, 62(3, Zokango), 653-662 (Japanese) 2007. CODEN: SAIGAK. ISSN: 0370-8241. Publisher: Saishin Igakusha.
AB A review on action mechanism, preclin. study, and clin. development of anti-VEGF monoclonal antibody: bevacizumab (Avastin), and anti-EGFR monoclonal antibody: cetuximab (IMC-C225, Erbitux), panitumumab (ABX-EGF, Vectibix), and matuzumab (EMD72000) for treatment of colorectal cancer.

L20 ANSWER 10 OF 22 SCISEARCH COPYRIGHT (c) 2008 The Thomson Corporation on STN
2007:283153 The Genuine Article (R) Number: 142ML. The new paradigm in the treatment of colorectal cancer: are we hitting the right target?. Baranda, Joaquina; Williamson, Stephen (Reprint). Univ Kansas, Med Ctr, Div Hematol Oncol, Mail Stop 1044, 3901 Rainbow Blvd, Kansas City, KS 66160 USA (Reprint); Univ Kansas, Med Ctr, Div Hematol Oncol, Kansas City, KS 66160 USA. EXPERT OPINION ON INVESTIGATIONAL DRUGS (MAR 2007) Vol. 16, No. 3, pp. 311-324. ISSN: 1354-3784. Publisher: INFORMA HEALTHCARE, TELEPHONE HOUSE, 69-77 PAUL STREET, LONDON EC2A 4LQ, ENGLAND. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The treatment of advanced colorectal cancer has definitely advanced in the last 10 years as newer and more active cytotoxic chemotherapy agents have become available. Better understanding of different fundamental molecular changes in carcinogenesis has resulted in the emergence of important therapeutic targets in colon cancer treatment. The era of nihilism has been replaced by a time of optimism with the development of targeted therapy, with the promise of agents with improved activity and a better toxicity profile in the management of colon cancer. This review focuses on novel agents, particularly targeted therapy in both earlier and more advanced phases of clinical investigations.

L20 ANSWER 11 OF 22 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN
2007562838 EMBASE [Growth factors of the EGF family and their receptors]. Les facteurs de croissance de la famille de l'EGF et leurs recepteurs. Hubert, Pierre (correspondence). Laboratoire d'Ingenierie des Systemes Macromole culaires (LISM), UPR 9027 du CNRS, Institut de Biologie Structurale et Microbiologie, 31 chemin Joseph-Aiguier, 13402 Marseille Cedex 20, phubert@ibsm.cnrs-mrs.fr.
Bulletin du Cancer Vol. 94, No. SUPPL. 7, pp. F137-F145 Sep 2007.
Refs: 27.
ISSN: 0007-4551. E-ISSN: 1769-6917. CODEN: BUCABS
Pub. Country: France. Language: French. Summary Language: English; French.

Entered STN: 20071129. Last Updated on STN: 20071129
AB The growth factors that have been the first discovered and the best studied belong to the family of epidermal growth factors (EGF) and their receptors have also been the most studied and the best understood. The activation of these receptors occurs through their dimerisation, which induces a change of conformation leading to the unveiling of an intrinsic tyrosine kinase activity, which in turn generates tyrosine phosphate moieties on the receptor itself and on cytoplasmic protein substrates. The interactions between the eleven growth factors and their four receptors allow a considerable variety of effects according to the cell type and the message received. The main consequence is the generation of proliferation signals which may follow several transduction pathways, among which the MAP kinase and the PI3 kinase pathway are the best known. The oncogenic alterations of the growth factor - receptor interaction are multiple and constitute several potential targets for therapeutic development. .COPYRGT. John Libbey Eurotext.

L20 ANSWER 12 OF 22 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN
2007595746 EMBASE Evolvable signaling networks of receptor tyrosine kinases: Relevance of robustness to malignancy and to cancer therapy.
Amit, Ido; Yarden, Yosef (correspondence). Department of Biological Regulation, Weizmann Institute of Science, Rehovot, Israel. yosef.yarden@weizmann.ac.il. Wides, Ron. Mina and Everard Goodman Faculty of Life Sciences, Bar-Ilan University, Ramat Gan, Israel. Amit, Ido. Broad Institute of MIT and Harvard, 7 Cambridge Center, Cambridge, MA 02142, United States. Yarden, Yosef (correspondence). Department of Biological Regulation, Candiotty Building, Weizmann Institute of Science, 1 Hertzl Street, Rehovot 76100, Israel. yosef.yarden@weizmann.ac.il.
Molecular Systems Biology Vol. 3 2007. arn. 151
Refs: 95.
ISSN: 1744-4292. E-ISSN: 1744-4292.
MSB4100195. Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20071227. Last Updated on STN: 20071227
AB Robust biological signaling networks evolved, through gene duplications, from simple, relatively fragile cascades. Architectural features such as layered configuration, branching and modularity, as well as functional characteristics (e.g., feedback control circuits), enable fail-safe performance in the face of internal and external perturbations. These universal features are exemplified here using the receptor tyrosine kinase (RTK) family. The RTK module is richly mutated and overexpressed in human malignancies, and pharmaceutical interception of its signaling effectively retards growth of specific tumors. Therapy-induced interception of RTK-signaling pathways and the common evolvement of drug resistance are respectively considered here as manifestations of fragility and plasticity of robust networks. The systems perspective we present views pathologies as hijackers of biological robustness and offers ways for identifying fragile hubs, as well as strategies to overcome drug resistance. .COPYRGT. 2007 EMBO and Nature Publishing Group All rights reserved.

L20 ANSWER 13 OF 22 MEDLINE on STN DUPLICATE 3
2006364071. PubMed ID: 16777680. EGFR-targeted immunoliposomes derived from the monoclonal antibody EMD72000 mediate specific and efficient drug delivery to a variety of colorectal cancer cells. Mamot Christoph; Ritschard Reto; Kung Willy; Park John W; Herrmann Richard; Rochlitz Christoph F. (Division of Oncology, Department of Internal Medicine, University Hospital of Basel, Petersgraben 4, CH-4031 Basel, Switzerland.. mamotc@uhbs.ch) . Journal of drug targeting, (2006 May) Vol. 14, No. 4, pp. 215-23. Journal code: 9312476. ISSN: 1061-186X. Pub. country: England: United Kingdom. Language: English.
AB We hypothesized that immunoliposomes (ILs) constructed using Fab' from the

humanized anti-EGFR monoclonal antibody, EMD72000, can provide efficient intracellular drug delivery in EGFR-overexpressing colorectal tumor cells.ILs were constructed modularly with various MAb fragments, including Fab' from EMD72000 (matuzumab) or C225 (cetuximab, Erbitux) covalently linked to stabilized liposomes containing chemotherapeutic drugs or probes. Immunoliposome preparation was optimized, including Fab' reduction and linkage, and evaluated for specific binding and cytotoxicity in epidermal growth factor receptor (EGFR)--overexpressing colorectal cancer cell lines in vitro. Flow cytometry showed that EGFR-targeted ILs, but not non-targeted liposomes or irrelevant ILs, were efficiently bound and internalized by a variety of EGFR-overexpressing colorectal cancer cells. Linkage of the Fab' to a longer PEG chain (Mal-PEG3400-DSPE) resulted in an increased uptake of immunoliposomal constructs when compared to previously used materials (Mal-PEG2000-DSPE). ILs derived from EMD72000-Fab' were used to deliver doxorubicin to EGFR-overexpressing target cells in vitro. Immunoliposomal doxorubicin was significantly more cytotoxic than the corresponding non-targeted liposomal drug in target cells, such as HCT116, while equivalent in cells lacking EGFR-overexpression, such as Colo205. We conclude that EGFR-targeted ILs derived from the humanized MAb EMD72000 provide efficient and targeted delivery of anticancer drugs in colorectal cancer cells overexpressing EGFR.

L20 ANSWER 14 OF 22 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

2006:533650 Document No.: PREV200600524378. Novel targets in gastric and esophageal cancer. Valverde, Claudia Maria; Macarulla, Teresa; Casado, Esther; Javier Ramos, Francisco; Martinelli, Erika; Tabernero, Josep [Reprint Author]. Vall Hebron Univ Hosp, Med Oncol Program, P Vall Hebron 119-129, E-08035 Barcelona, Spain. jtabernero@vhebron.net. Critical Reviews in Oncology-Hematology, (AUG 2006) Vol. 59, No. 2, pp. 128-138. ISSN: 1040-8428. Language: English.

AB Esophageal cancer (EC) and gastric cancer (GC) constitute a major cause of cancer deaths worldwide. Recent improvements in both surgical techniques and adjuvant/neoadjuvant chemotherapy, radiotherapy or both have increased the survival of patients with loco-regional disease. However, most patients with GC or EC have advanced disease either at diagnosis or during the follow-up, and despite recent advances, these patients still do poorly. Understanding of the molecular pathways that characterize cell growth, cell cycle, apoptosis, angiogenesis and invasion has provided novel targets in cancer therapy. In this review we describe the current status of targeted therapies in the treatment of EC and GC, including EGFR inhibitors, antiangiogenic agents, cell cycle inhibitors, apoptosis promoters and matrix metalloproteinases inhibitors. The emerging data from the clinical development of these compounds has provided novel opportunities in the treatment of EC and GC that will probably translate into clinical benefit for patients with these common malignancies.

L20 ANSWER 15 OF 22 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

2007:259456 Document No.: PREV200700269523. Anti-EGFR immunoliposomes mediate specific and efficient drug delivery to target cells and can overcome multidrug-resistance. Mamot, Christoph [Reprint Author]; Kueng, Willy; Ritschard, Rem; Reuter, Juergen; Herrmann, Richard; Noble, Charles; Drummond, Daryl; Kirpotin, Dmitri; Rochlitz, Christoph; Park, John W.. Univ Basel Hosp, CH-4031 Basel, Switzerland. Proceedings of the American Association for Cancer Research Annual Meeting, (APR 2005) Vol. 46, pp. 334.
Meeting Info.: 96th Annual Meeting of the American-Association-for-Cancer-Research. Anaheim, CA, USA. April 16 -20, 2005. Amer Assoc Canc Res. ISSN: 0197-016X. Language: English.

L20 ANSWER 16 OF 22 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN DUPLICATE 4

2005217160 EMBASE Monoclonal antibodies targeting the epidermal growth factor receptor.

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Pub. Country: Netherlands. Language: English. Summary Language: English.

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AB The epidermal growth factor receptor (EGFR, HER1) autocrine pathway contributes to a number of highly relevant processes in cancer development and progression, including cell proliferation, regulation of apoptotic cell death, angiogenesis and metastatic spread. The crucial role that EGFR plays in human cancers has led to an extensive search for selective inhibitors of its signaling pathway. The results of a large body of preclinical studies and clinical trials thus far conducted suggest that targeting the EGFR could bring a significant contribution to cancer therapy. A variety of different approaches are currently being used to target the EGFR. The most promising strategies in clinical development include monoclonal antibodies, to prevent ligand binding, and small molecules inhibitors of the tyrosine kinase enzymatic activity, that inhibit autophosphorylation and downstream intracellular signaling. Several blocking monoclonal antibodies against the EGFR have been developed. Among these, IMC-225 is a chimeric human-mouse monoclonal IgG1 antibody that has been the first anti-EGFR targeted therapy to enter clinical evaluation in cancer patients in Phase II and III studies, alone or in combination with conventional radiotherapy and chemotherapy. However, other antibodies against EGFR have demonstrated antitumor activity in several preclinical models of human cancer and are currently under investigation in the clinical setting, such as ICR62, ABX-EGF and EMD72000. This review will focus on all the preclinical data available on monoclonal antibodies engineered against the EGF receptor. .COPYRGT. 2005 Bentham Science Publishers Ltd.

L20 ANSWER 17 OF 22 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

2005:192105 Document No.: PREV200500196815. Blockade of epidermal growth factor receptor (EGFR) activity. Jimeno, Antonio; Hidalgo, Manuel [Reprint Author]. Sidney Kimmel Comprehens CAnc Ctr, Johns Hopkins Univ, Bunting Blaustein Canc REs Bldg,Room 1M88,1650 Or, Baltimore, MD, 21231, USA. mhidalg1@jhmi.edu. Critical Reviews in Oncology-Hematology, (March 2005) Vol. 53, No. 3, pp. 179-192. print.

ISSN: 1040-8428. Language: English.

L20 ANSWER 18 OF 22 MEDLINE on STN

2005043487. PubMed ID: 15523683. Magnetic resonance imaging in an orthotopic rat model: blockade of epidermal growth factor receptor with EMD72000 inhibits human pancreatic carcinoma growth. Bangard Christopher; Gossmann Axel; Papyan Armine; Tawadros Samir; Hellmich Martin; Bruns Christiane J. (Department of Radiology, University of Cologne, Cologne, Germany.. cbangard@gmx.de) . International journal of cancer. Journal international du cancer, (2005 Mar 10) Vol. 114, No. 1, pp. 131-8. Journal code: 0042124. ISSN: 0020-7136. Pub. country: United

States. Language: English.

AB The purpose of our research was to investigate the antiangiogenic effect of the epidermal growth factor receptor monoclonal antibody (anti-EGF-R MAB) EMD72000, in an orthotopic human pancreatic carcinoma model in rats, assessed by magnetic resonance (MR) imaging using angiogenic surrogate markers in comparison with histopathologic findings. Human pancreatic adenocarcinoma cells L3.6pl were injected orthotopically in the pancreas of 12 athymic nude rats. Through a 21-day course, groups of 6 rats were treated intraperitoneally with either EMD72000 or with saline solution for control animals. Dynamic contrast-enhanced MR imaging was performed before and after the treatment to assess microvascular permeability, estimated by the endothelial transfer coefficient (KPS) and fractional plasma volumes (fPV) of the pancreatic tumors. EMD72000-treated animals showed significantly less tumor volume progression (1,080 mm3 +/- 1,244; p = 0.012) and significantly lower values for microvascular permeability (KPS = 4.2 ml min(-1) 100 ml(-1) of tissue +/- 2.8; p = 0.015), fractional plasma volume (fPV = 0.018 ml ml(-1) of tissue +/- .015; p = 0.003) and microvessel density (MVD = 13 +/- 4 (0.159 mm2); p = 0.001) than saline-treated animals (6,544 mm3 +/- 5,202; 9.5 ml min(-1) 100 ml(-1) of tissue +/- 4.3, 0.056 ml ml(-1) of tissue +/- 0.019 and 25 +/- 5 (0.159 mm2), respectively). KPS and fPV values showed moderate positive correlation with MVD (r = 0.5, p = 0.103; r = 0.6, p = 0.065, respectively). Intraperitoneal injection of EMD72000 inhibits orthotopic human pancreatic carcinoma growth in rats. Antiangiogenic effects of anti-EGF-R MAB EMD72000 can be quantified and monitored noninvasively by dynamic MR imaging.

L20 ANSWER 19 OF 22 MEDLINE on STN DUPLICATE 5

2005088306. PubMed ID: 15717942. Clinical experience with monoclonal antibodies to epidermal growth factor receptor. Calvo Emiliano; Rowinsky Eric K. (Institute for Drug Development, Cancer Therapy and Research Center, University of Texas Health Science Center at San Antonio, 7979 Wurzbach Road, 4th Floor, Zeller Building, San Antonio, TX 78229, USA.) Current oncology reports, (2005 Mar) Vol. 7, No. 2, pp. 96-103. Ref: 58. Journal code: 100888967. ISSN: 1523-3790. Pub. country: United States. Language: English.

AB Recent knowledge about the intermediate steps and final consequences of ligand-dependent epidermal growth factor receptor (EGFR) activation has clearly supported the notion that EGFR plays a fundamental role in regulating the proliferation and survival of malignant neoplasms. Among the rationally designed target-based therapeutics that are being assessed, those targeting EGFR appear to be some of the most clinically relevant. The strategy of using monoclonal antibodies (mAbs) to block ligand binding to the extracellular domain of the EGFR has led to the development of therapeutics that robustly arrest malignant cell proliferation and, in some cases, induce profound tumor regression. The chimeric mAb against EGFR, cetuximab, has already been approved by regulatory agencies worldwide to treat patients with advanced colorectal cancer. Other mAbs against EGFR, particularly panitumumab (ABX-EGF), h-R3, and EMD72000, are in advanced stages of clinical development.

L20 ANSWER 20 OF 22 MEDLINE on STN

2004004944. PubMed ID: 14701780. Phase I study of the humanized antiepidermal growth factor receptor monoclonal antibody EMD72000 in patients with advanced solid tumors that express the epidermal growth factor receptor. Vanhoefer Udo; Tewes Mitra; Rojo Federico; Dirsch Olaf; Schleucher Norbert; Rosen Oliver; Tillner Joachim; Kovar Andreas; Braun Ada H; Trarbach Tanja; Seeber Siegfried; Harstrick Andreas; Baselga Jose. (Department of Internal Medicine (Cancer Research), West German Cancer Center, University of Essen Medical School, Hufelandstrasse 55, 45122 Essen, Germany.. udo.vanhoefer@uni-essen.de) . Journal of clinical oncology : official journal of the American Society of Clinical Oncology,

(2004 Jan 1) Vol. 22, No. 1, pp. 175-84. Journal code: 8309333. ISSN: 0732-183X. Pub. country: United States. Language: English.

AB PURPOSE: To investigate the safety and tolerability and to explore the pharmacokinetic and pharmacodynamic profile of the humanized antiepidermal growth factor receptor monoclonal antibody EMD72000 in patients with solid tumors that express epidermal growth factor receptor (EGFR). PATIENTS AND METHODS: This was a phase I dose-escalation trial of EMD72000 in patients with advanced, EGFR-positive, solid malignancies that were not amenable to any established chemotherapy or radiotherapy treatment. EMD72000 was administered weekly without routine premedication until disease progression or unacceptable toxicity. RESULTS: Twenty-two patients were treated with EMD72000 at five different dose levels (400 to 2,000 mg/wk). National Cancer Institute common toxicity criteria grade 3 headache and fever occurring after the first infusion were dose limiting at 2,000 mg/wk; thus, the maximum-tolerated dose was 1,600 mg/wk. No other severe side effects, especially no allergic reactions or diarrhea, were observed. Acneiform skin reaction was the most common toxicity, but it was mild, with grade 1 in 11 patients (50%) and grade 2 in three patients (14%). Pharmacokinetic analyses demonstrated a predictable pharmacokinetic profile for EMD72000. Pharmacodynamic studies on serial skin biopsies revealed that EMD72000 effectively abrogated EGFR-mediated cell signaling (eg, reduced phosphorylation of EGFR and mitogen-activated protein kinase), with no alteration in total EGFR protein. Objective responses (23%; 95% CI, 8% to 45%) and disease stabilization (27%; 95% CI, 11% to 50%) were achieved at all dose levels, and responding patients received treatment for up to 18 months without cumulative toxicity. CONCLUSION: Treatment with EMD72000 was well tolerated and showed evidence of activity in heavily pretreated patients with EGFR-expressing tumors. EMD72000 at the investigated doses significantly inhibited downstream EGFR-dependent processes.

L20 ANSWER 21 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN

2003:511168 Document No. 139:74057 Lyophilized preparation containing antibodies to the EGF receptor. Mahler, Hanns-Christian; Zobel, Hans-Peter; Mueller, Robert; Bachmann, Christiane; Haas, Udo; Krueger, Ludwig; Martini-Marr, Ulrike (Merck Patent GmbH, Germany). PCT Int. Appl. WO 2003053465 A2 20030703, 32 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (German). CODEN: PIXXD2. APPLICATION: WO 2002-EP13223 20021125. PRIORITY: DE 2001-10163459 20011221.

AB The invention relates to a lyophilized, pharmaceutical preparation containing an antibody to the receptor of the endothelial growth factor (EGF receptor). The preparation has an improved storage stability, even at high temps. and once reconstituted, can be used parenterally for the treatment of tumors. Thus a lyophilizate that was obtained from an aqueous solution contained: EMD 72000 10 mg/mL; potassium phosphate buffer pH 7.2 10 mmol/L; arginine 17 mmol/L; saccharose 3 weight/weight%; polyoxyethylene(20)-sorbitan monolaurate 0.01 weight/weight%; PEG 6000 0.4 weight/weight%.

L20 ANSWER 22 OF 22 MEDLINE on STN DUPLICATE 6

2003340206. PubMed ID: 12850190. Inhibitors of epidermal-growth-factor receptors: a review of clinical research with a focus on non-small-cell lung cancer. Sridhar Srikala S; Seymour Lesley; Shepherd Frances A.

(Division of Medical Oncology, Department of Medicine of the University Health Network, Princess Margaret Hospital and the University of Toronto, Canada.) The lancet oncology, (2003 Jul) Vol. 4, No. 7, pp. 397-406. Ref: 73. Journal code: 100957246. ISSN: 1470-2045. Pub. country: England: United Kingdom. Language: English.

AB Despite aggressive surgical and chemotherapeutic interventions, non-small-cell lung cancer (NSCLC) is the leading cause of cancer-related death in men and women with overall cure rates of less than 15%. Recent advances in our understanding of cellular signalling and its critical role in tumorigenesis has led to the development of novel therapies which may offer new hope. In particular, the epidermal growth-factor receptor superfamily is an attractive therapeutic target because it is commonly overexpressed in malignant disease, regulates many vital cellular processes, and seems to be a negative prognostic indicator. Several selective inhibitors of this family of receptors are currently being evaluated in several cancers including NSCLC. In this review we examine current preclinical and clinical evidence on monoclonal antibodies (cetuximab, ABX-EGF, EMD72000, MAb ICR62, h-R3, MDX-447, MDX-H210, trastuzumab, and 2C4), immunoconjugates (Y10, Ua30:2, Mab806), anti-EGF vaccine (YMB2000), and tyrosine kinase inhibitors (gefitinib, erlotinib, CI1033, GW572016, EKB 569, PKI166, PD158780, and TAK 165).

=> s "humanized Mab 425"
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L22 ANSWER 1 OF 1 MEDLINE on STN DUPLICATE 1
1995291130. PubMed ID: 7773132. Distribution of humanized MAb 425 (EMD 62,000) in rats and specific localization in tumor-bearing nude mice. Steiner K; Haunschild J; Faro H P; Senekowitsch R. (E. MERCK, Institute of Pharmacokinetics and Metabolism, Grafing, Germany.) Cellular and molecular biology (Noisy-le-Grand, France), (1995 Feb) Vol. 41, No. 1, pp. 179-84. Journal code: 9216789. ISSN: 0145-5680. Pub. country: France. Language: English.

AB The murine MAb 425 (IgG2a) directed against human epidermal growth factor receptor is considered to have therapeutic potential in glioma patients. In order to circumvent immune response in clinical use, the MAb 425 was humanized by CDR-grafting (IgG1). We have studied the distribution of reshaped MAb 425 (EMD 62,000) in Wistar rats and the specific localization in female nude mice bearing human mamma carcinoma xenografts. The 125I-labelled MAb 425 was administered intravenously in a single dose (1 mg/kg) using unspecific human IgG1 antibody as control. The biodistribution was investigated both quantitatively and by whole-body autoradiography. The autoradiographs showed a selective uptake of radioactivity by the tumour tissue. 15 days after administration, radioactivity was bound exclusively to the tumour. Similar results were obtained with the murine monoclonal antibody. Quantitative studies exhibited a tumour-blood ratio of about 5. The study demonstrates that the humanized MAb 425 is selectively localized in human mamma carcinoma xenografted to athymic mice.

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L24 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2008 ACS on STN
2004:333597 Document No. 140:344924 Bispecific anti-ErbB antibodies and their use in tumor therapy. Kreysch, Hans-Georg (Merck Patent GmbH, Germany). PCT Int. Appl. WO 2004032961 A1 20040422, 52 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-EP11165 20031009. PRIORITY: EP 2002-22389 20021010; EP 2002-22390 20021010.
AB The invention relates to novel bispecific antibodies and their use in tumor therapy. The novel antibodies have the ability to bind to ErbB receptors, preferably ErbB1 receptors, which are overexpressed on many cancer tissues. Since the different specificities of the antigen-binding sites are directed to different epitopes within the binding domain of same or different ErbB receptors, these antibodies are more effective with respect to inhibition and down-regulation of the ErbB receptor and the corresponding signaling cascade. For example, preparation of F(ab')2 fragments of humanized monoclonal antibodies MAb 425 and chimeric MAb 225 was presented.

L24 ANSWER 2 OF 4 MEDLINE on STN DUPLICATE 1
1999163421. PubMed ID: 10068277. Epidermal growth factor receptor inhibition by a monoclonal antibody as anticancer therapy. Mendelsohn J. (University of Texas M.D. Anderson Cancer Center, Houston, Texas 77030, USA.) Clinical cancer research : an official journal of the American Association for Cancer Research, (1997 Dec) Vol. 3, No. 12 Pt 2, pp. 2703-7. Ref: 48. Journal code: 9502500. ISSN: 1078-0432. Pub. country: United States. Language: English.
AB Monoclonal antibody (mAb) 225 against the human epidermal growth factor receptor blocks activation of receptor tyrosine kinase. This retards or arrests cell cycle progression, with accumulation of cells in G1 phase. The mechanism of growth inhibition involves increased levels of p27KIP1 and inhibition of cyclin-dependent kinase-2 activity. mAb in combination with chemotherapy exhibits a synergistic antitumor activity, with successful eradication of well-established tumor xenografts that resist treatment with either mAb or drug alone. A Phase I clinical trial has established the safety of repeated administration of human:mouse chimeric mAb 225 at concentrations that maintain receptor-saturating blood levels for up to 3 months. Phase I trials exploring mAb 225 treatment in combination with doxorubicin, cisplatin, or paclitaxel are ongoing.

L24 ANSWER 3 OF 4 MEDLINE on STN DUPLICATE 2
1994193211. PubMed ID: 8144194. Mechanisms of cellular cytotoxicity mediated by a recombinant antibody-IL2 fusion protein against human melanoma cells. Naramura M; Gillies S D; Mendelsohn J; Reisfeld R A; Mueller B M. (Scripps Research Institute, La Jolla, CA 92037.) Immunology letters, (1993 Dec) Vol. 39, No. 1, pp. 91-9. Journal code: 7910006. ISSN: 0165-2478. Pub. country: Netherlands. Language: English.
AB Functional characteristics were established for a genetically engineered fusion protein between human IL2 and mouse/human chimeric mAb 225 directed against human epidermal growth factor receptor (EGFR), aberrantly expressed on human melanoma cells. The

emphasis of these studies was on the mechanism(s) of action by which the ch225-IL2 fusion protein mediated cytotoxic killing of human melanoma cells by different human immune effector cells. Ch225-IL2 fusion protein bound to human EGFR with the high affinity of the parental antibody, and was as active as the equivalent amount of rhIL2. Ch225-IL2 enhanced cellular cytotoxicity mediated by freshly separated PBMC, isolated natural killer (NK) cells and activated T cells against melanoma cell lines. NK cells, which constitutively express both Fc gamma RIII and IL2R, interacted with ch225-IL2, mainly through Fc gamma RIII, while the involvement of IL2R was secondary. However, the effect of ch225-IL2 on activated T cells was most likely mediated through IL2R. These results suggest that the genetically engineered ch225-IL2 fusion protein may become a potent immunotherapeutic agent capable of stimulating various immune effector populations to effectively kill human melanoma cells.

L24 ANSWER 4 OF 4 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
1994:127878 Document No.: PREV199497140878. Mechanisms of cellular cytotoxicity mediated by a recombinant antibody-IL2 fusion protein against human melanoma cells. Naramura, Mayumi; Gillies, Stephen D.; Mendelsohn, John; Reisfeld, Ralph A.; Mueller, Barbara M. [Reprint author]. Scripps Res. Inst., Dep. Immunol., IMM13, 10666 N. Torrey Pines Road, La Jolla, CA 92037, USA. Immunology Letters, (1993 (1994)) Vol. 39, No. 1, pp. 91-99. . CODEN: IMLED6. ISSN: 0165-2478. Language: English.

AB Functional characteristics were established for a genetically engineered fusion protein between human IL2 and mouse/human chimeric mAb 225 directed against human epidermal growth factor receptor (EGFR), aberrantly expressed on human melanoma cells. The emphasis of these studies was-on the mechanism(s) of action by which the ch225-IL2 fusion protein mediated cytotoxic killing of human melanoma cells by different human immune effector cells. Ch225-IL2 fusion protein-bound to human EGFR. with the high affinity of the parental antibody, and was as active as the equivalent amount of rhIL2. Ch225-IL2 enhanced cellular cytotoxicity mediated by freshly separated PBMC, isolated natural killer (NK) cells and activated T cells against melanoma cell lines. NK cells, which constitutively express both Fc-gamma-RIII and IL2R, interacted with ch225-IL2, mainly through Fc-gamma-RIII, while the involvement of IL2R was secondary. However, the effect of ch225-IL2 on activated T cells was most likely mediated through IL2R. These results suggest that the genetically engineered ch225-IL2 fusion protein may become a potent immunotherapeutic agent capable of stimulating various immune effector populations to effectively kill human melanoma cells.

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